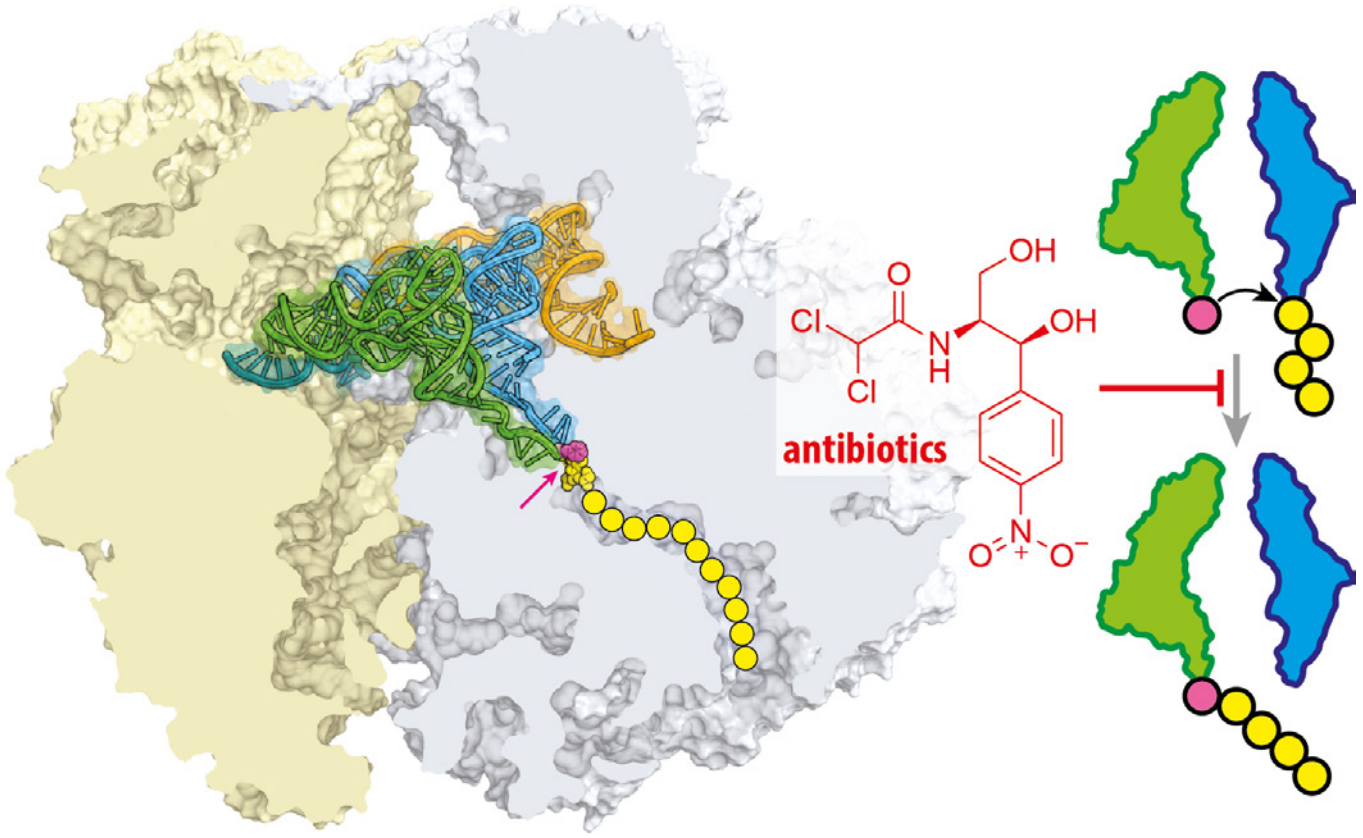
universität innsbruck

Research Area
Center for Molecular Biosciences (CMBI)

scientific report 2022–2024



Scientific Coordinators

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imprint

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Cover figure:
The cover illustrates the location of the antibiotic's action within the peptidyl transfer center of the ribosome (magenta arrow). Various antibiotics that target the ribosome inhibit the reaction that forms peptide bonds, which is catalyzed by the peptidyl transferase center. The chemical structure of one such antibiotic (chloramphenicol) is depicted in red (adapted from Syroegin, E.A., Flemmich, L., Klepacki, D., Vazquez-Laslop, N., Micura, R. and Polikanov, Y.S. (2022) Structural basis for the context-specific action of the classic peptidyl transferase inhibitor chloramphenicol. *Nat. Struct. Mol. Biol.*, **29**, 152–161).

The "Center for Molecular Biosciences Innsbruck (CMBI)" – a life science network in western Austria

The present report, covering the years 2022 to 2024, highlights recent scientific breakthroughs, the latest developments in ongoing research projects, and outstanding achievements by members of the Center for Molecular Biosciences at the University of Innsbruck (CMBI). As one of the most dynamic and exciting fields in modern research, molecular biosciences aim to achieve a comprehensive understanding of cellular processes by bridging the gap between the properties of isolated molecules and their various functions in living organisms. For example, even small changes in the conformation or constitution of bioactive molecules such as DNA, RNA, and proteins can profoundly affect the state of cells, microorganisms, plants, animals, and humans, with implications for health and disease. Recent technological advances in microscopic imaging, new generation sequencing applications, and tools for analyzing molecular structure are providing a wealth of information that is critical for a detailed understanding of biological systems and human health. The CMBI aims to provide an interdisciplinary platform to address key research questions in the rapidly evolving field of molecular biosciences, to foster collaborative projects with added value, and to increase the international visibility of the CMBI and its members.

The CMBI currently consists of 29 internationally competitive research teams from three faculties (Chemistry and Pharmacy; Biology; Mathematics, Informatics and Physics) whose activities are focused on research and teaching. CMBI members head the EC Horizon–2020 programs MESI-STRAT (2018-2023), ARDRE (2019-2025), CRAFTMOL (2022-2027), AGEMEC (2019-2023), and the FWF doc:fund program CavX (2023-2027) and contribute to the FWF special programs SFB-F80 RNA-Deco- and SFB-F78 NeuroStemModulation (2020-2028). Notably, several members have initiated the CMBI-embedded University PhD programs "Ageing and Regeneration" and "Calcium channels in excitable cells". Moreover, CMBI members were able to successfully compete in the FFG 2023 call for university infrastructure and were approved for state-of-the-art instrumentation, a Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometer in 2024 (2.4 Mio €). In addition, funding from the University of Innsbruck has enabled the installation of a new console for the 600 MHz NMR instrumentation (0.6 Mio €) and a new scanning electron microscope (1.0 Mio €). These infrastructures will significantly advance biomolecular structural analysis and thus the life sciences in the Western Austrian region. In order to further strengthen the life sciences community in Tyrol, and to provide new career perspectives for young scientists, the CMBI is a co-organizer of the internationally visible Innsbruck Life Science Meetings.

The CMBI coordinators:
Ronald Micura Alexandra Koschak Frank Edenhofer

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>> CMBI facts

The Center for Molecular Biosciences (CMBI) at the University of Innsbruck is an integrative and multidisciplinary research and teaching institution. The mission of the CMBI is to advance studies on the structure, function, and interaction of biological macromolecules and low molecular weight compounds relevant for cellular growth, metabolism, and development. The research activities in the CMBI take advantage of existing research strength in different fields and have strongly promoted interdisciplinary research activities in five major fields of biomolecular sciences.

Basic and applied biomolecular research fields at the CMBI

- Structure, dynamics and interactions of biologically important molecules
- Molecular basis of physiological and pathophysiological processes
- Metabolites, natural and synthetic compounds that modulate important biological processes
- Cell-to-cell communication and cellular function
- Development, regeneration and aging of whole organisms

Twenty-nine research groups from the Faculty of Chemistry and Pharmacy, the Faculty of Biology, and the Faculty of Mathematics, Informatics & Physics are members of the CMBI.

members

CMBI members	Areas of expertise
	Chemistry
K. Breuker	biomolecular mass spectrometry
C. Huck	bioanalytics
C. Kreutz	biomolecular NMR spectroscopy
K. Liedl	theoretical chemistry, computer-aided molecular design
T. Magauer	synthetic organic chemistry
R. Micura	organic chemistry and chemical biology
T. Müller, B. Kräutler	organic and bioorganic chemistry
E. Stefan, M. Hartl	biochemistry, molecular genetics
K. Thedieck, M. Kwiatkowski	biochemistry, cell biology
M. Tollinger	biomolecular NMR spectroscopy
	Pharmacy
M. Ganzera, H. Stuppner	pharmaceutical biology, phytochemistry
T. Kaserer	computational chemistry, molecular modelling
A. Koeberle	molecular pharmacology
A. Koschak	cell biology, molecular sensory physiology and pharmacology
S. Moser	pharmaceutical biology
M. Spetea	pharmaceutical chemistry, drug design
J. Striessnig, N. Singewald	cell biology, neuropharmacology
P. Tuluc	cell biology, molecular endocrinology
	Biology
R. Dallinger	cell physiology, ecotoxicology
F. Edenhofer	stem cell biology
B. Hobmayer, P. Ladurner	cell and developmental biology
M. Höckner	molecular biology, cell physiology
P. Jansen-Dürr	cell biology, molecular biology
I. Kranner	plant physiology, biochemistry
J. Mertens	neural aging
D. Meyer, R. Kimmel	developmental biology
A. Sandbichler, T. Schwerte	cell biology, cell physiology
W. Zwerschke	molecular cell biology
	Physics
S. Denifl	biophysics, radiation physics

As a graduate teaching and postdoctoral training institution, the CMBI has a strong mission. Several early-career scientists have been recognized for their achievements, including Fabian Jürgen Hammerle (2023) and Isabel Dittmann (2024) who received the Award of Excellence from the Austrian Federal Ministry of Education, Science and Research and Matthias Ganglberger (2023) who received a scholarship of the Austrian Academy of Sciences, as well as several poster prizes at international conferences. For example, Michaela Egger (2022) received the IRT Poster Prize at the International Round Table on Nucleosides, Nucleotides and Nucleic Acids in Stockholm. Several prestigious postdoctoral fellowships were awarded, including to Ondrej Kovac (Experientia Fellowship, 2020), Tobias Pinkert (Esprit Fellowship, 2020) and Przemek Wanat (Esprit Fellowship, 2022), as well as a Young Scientists Best Paper Award (Springer, 2023) to Sarah Moreno. Nadine Ortner also received the Heribert Konzett Award 2023, which is awarded annually by the Austrian Pharmacological Society (APHAR) to honour the outstanding achievements of young scientists conducting independent research. Furthermore, eighteen research projects for young CMBI researchers were approved by the Tiroler Wissenschaftsförderung (TWF).

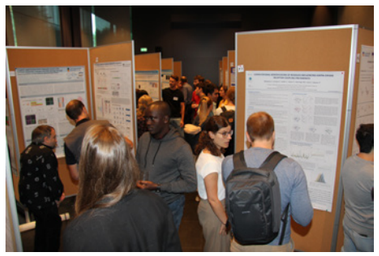
CMBI scientists are members of the Austrian Academy of Sciences (Bernhard Kräutler, Ronald Micura, Jörg Striessnig) and of the German Academy of Sciences, Leopoldina (Bernhard Kräutler, Jörg Striessnig). Ilse Kranner has been Board Member of the Austrian Science Fund (FWF) for the discipline of biology and Ronald Micura for the discipline of organic chemistry. The activities of the CMBI are currently coordinated by Ronald Micura (head), Alexandra Koschak and Frank Edenhofer.

In the years 2022 - 2024 the CMBI member labs published 527 papers in peer reviewed journals. This includes **60** publications in the world leading journals *Nature, Cell, Proceedings of the National Academy of Sciences of the United States of America, Nature Communication, Nature Biotechnology, Nature Ecology & Evolution, Nature Medicine, Nature Cell Biology, Nature Microbiology, Nature Structural & Molecular Biology, Science Translational Medicine, Cell Stem Cell, Cell Metabolism, Cell Discovery, Brain, Cancer Cell, Immunity, Nucleic Acids Research, Advanced Science,* and in top journals of chemistry and physics, including *Journal of the American Chemical Society, Angewandte Chemie International Edition, Chemical Science, and Accounts of Chemical Research*. The total amount of third-party funding since 2022 amounts to more than 41 million EUR. Modern infrastructure obtained through special governmental funding for research equipment significantly strengthens research in structural chemistry and biology, bioanalytics, and biophysics at the CMBI.

https://www.uibk.ac.at/de/newsroom/2024/cmbi-wurde-heuer-20/

>> CMBI turned 20 years old

The Center for Molecular Biosciences Innsbruck (CMBI) at the University of Innsbruck celebrated its 20th anniversary in 2024 with the 9th CMBI Meeting, which took place at the Congress Park Igls.



In recent years, the CMBI has established itself as an important component of biomolecular and biomedical research in Austria and enjoys a high level of international visibility. It brings together researchers from a wide range of scientific disciplines, from molecular biology and genetics to chemistry, pharmacy and biophysics. Together, they focus primarily on the structure, function and interaction of biological macromolecules and small molecules for cell growth, metabolism and the development of organisms. The CMBI was founded 20 years ago as part of the newly established Research Focus System of the University of Innsbruck. In 2004, the first CMBI meeting took place at the Grillhof in Vill, organized by Klaus Bister, Bernd Pelster and Jörg Striessnig. Today, 29 research groups from the Faculties of Biology, Chemistry and Pharmacy as well as Mathematics, Physics and Computer Science are involved.

The 9th CMBI meeting, organized by Ronald Micura, Frank Edenhofer and Alexandra Koschak, took place at the end of September 2024 and featured a number of high-calibre guest speakers, including Henry Colecraft from Columbia University, Stefano Pluchino from the University of Cambridge and Jieping Zhu from the EPF Lausanne. Recent results from various research groups involved in the CMBI were also presented. The poster prizes for young scientists were again awarded during the meeting. The winners were Yuliia Nikonishyna from the Department of Pharmacology and Toxicology at the Institute of Pharmacy, Anna Ploner from the Institute of Organic Chemistry, Sandra Senn from the Institute of Molecular Biology, Immanuel Plangger from the Institute of Organic Chemistry and Angeliki Spathopoulou from the Institute of Molecular Biology.

The specific research topics of the 29 CMBI member labs are listed below.

Research topics

Research topics
• Metabolic signaling, multi-omics (K. Thedieck, M. Kwiatkowski)
• Functional lipidomics, molecular phytopharmacology (Koeberle)
• Proteomics, metabolomics, phytomics (Bonn, Huck)
• Regulation of cell function by protein modification (Schneider)
• Oncogenic transcription factors and their cellular targets (Stefan, Hartl)
• Development of theoretical and computational methods describing molecular interactions in chemical and biological systems (Liedl)
• Biomolecular interactions in solution – NMR spectroscopy (Kreutz, Tollinger)
• Biomolecular interactions in the gas phase – mass spectrometry (Breuker)
• Synthesis, structure, function and interactions of RNA (Micura)
• Natural product synthesis, total synthesis, synthetic methods (Magauer)
• Natural products chemistry, pigments of life (Kräutler, Müller)
• Inelastic interaction of low energy electrons with molecules of biological relevance (Denifl)
• Bioactive natural products from the plant kingdom (Ganzera, Stuppner)
• Analysis, bioactivity, and target deconvolution of secondary metabolites (Moser)
• Development of selectively acting antitumor drugs (Kaserer)
• Development of potential drugs interacting with opioid receptors (Spetea)
• Ion channels as new drug targets and the neuropathological basis of anxiety disorders (Striessnig, Singewald)
• Ion channels in retinal physiology, diseases and pharmacotherapy (Koschak)
• Ion channels structure-function and their role in hormone release (Tuluc)
• Molecular and genetic control of vertebrate development (Meyer, Kimmel)
• Stem cell differentiation, regeneration and bioadhesion in basal Metazoa (Hobmayer, Ladurner)
• Neural reprogramming to study brain aging and neurological disorders (Mertens)
• Stem cell biology, cellular reprogramming & regeneration (Edenhofer)
• Biology of aging, mitochondrial physiology (Jansen-Dürr)
• Stress metabolites and signaling pathways in plants (Kranner)
• Cell ion and volume homeostasis and metabolic activity (Sandbichler, Schwerte)
• Stress response and immunity, epigenetics and gene regulation (Höckner)
• Trace element homeostasis in animal cells (Dallinger)
• Role of adipose tissue in obesity and ageing (Zwerschke)

CMBI SPECIALS – Research programs and infrastructure funding


picture: Otto Peter

>> JOINT RESEARCH ON CALCIUM CHANNELS – FWF funded PhD program


https://cavx.at/

In electrically excitable cells such as nerves, muscles and endocrine cells, voltage-dependent calcium channels regulate a variety of vital functions such as synaptic transmission, sensory processes such as hearing and vision, muscle contractions and the release of hormones. Malfunctions of these cell membrane proteins underlie many pathological conditions such as autism, Parkinson's disease, diabetes mellitus, retinal diseases, hearing loss and muscle weakness.

The Innsbruck Calcium Channel Research Cluster, consisting of eleven research groups based at both Innsbruck universities, has made significant progress in understanding how different calcium channels work, for example how they regulate cellular functions in healthy people and in disease and what pharmacological potential they have. In 2023, seven of the research groups including four CMBI members (Petronel Tuluc, Alexandra Koschak, Klaus Liedl, Dirk Meyer) were awarded a FWF doc.funds program to tackle a whole range of new questions as part of the International CavX PhD Program (https://cavx.at/).

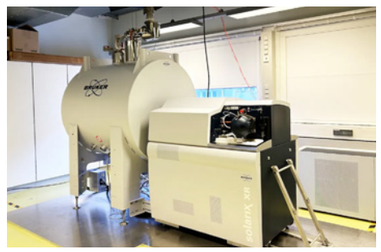
"I think our research network is a great opportunity for any PhD student. I don't know of any other place in the world where so many research teams work together so intensively and investigate the many different aspects of calcium channels in such a concentrated but complementary way. Every day we learn something new and we go one step further. I really enjoy that," emphasizes Petronel Tuluc who coordinates the consortium.

>> ERC ADVANCED GRANT – 'BEYOND STRESS'


https://www.uibk.ac.at/de/newsroom/2022/drei-hochdotierte-erc-advanced-grants/

In 2022, the CMBI member and biochemist Kathrin Thedieck was awarded an ERC Advanced Grant, the highest European funding for established scientists in basic research. Her research group investigates the regulation of metabolism by complex signaling networks in order to study fundamental cellular mechanisms of metabolic signal transduction experimentally and theoretically.
The protein mTOR controls virtually all metabolic processes in cells and organisms and is a key therapeutic target molecule in age-associated diseases such as cancer and neurodegenerative disorders. mTOR is at the center of a complex cellular signaling and metabolic network. In response to growth factors, nutrients, energy and stress, mTOR promotes metabolic processes that control cell growth and differentiation. But how are specific metabolic responses to specific metabolic signals mediated? Kathrin Thedieck wants to answer this question with her research. She and her team recently observed that proteins from so-called stress granules interact with mTOR beyond stress and control mTOR-dependent metabolic processes. With her BEYOND STRESS project, she is investigating this phenomenon and its significance for the functions of healthy cells and in tumors.
Kathrin Thedieck was Professor and Head of the Institute of Biochemistry at the University of Innsbruck until 2024, when she accepted an offer to become Professor of Molecular and Chemical Cell Biology at the University of Duisburg-Essen.

>> NEW MASS SPECTROMETER FOR BIOMOLECULAR RESEARCH

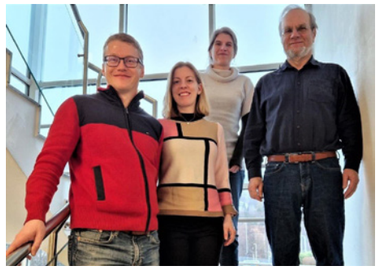

https://www.uibk.ac.at/en/newsroom/2025/new-mass-spectrometer-for-biomolecular-research/

Researchers at the Center for Molecular Biosciences (CMBI) have been awarded funding for a state-of-the-art mass spectrometer in a competitive FFG infrastructure call. The high-resolution 12 Tesla Fourier Transform-Ion Cyclotron Resonance (FT-ICR) instrument will open new avenues in biomolecular mass spectrometry with focus on ribonucleic acids (RNA), further strengthening the internationally recognized RNA hotspot in Innsbruck and advancing research in nucleic acid chemistry and biology. The acquisition is the result of a joint initiative of Kathrin Breuker (lead), together with Christoph Kreutz, Ronald Micura, Martin Tollinger, Thomas Müller and Thomas Magauer from the Department of Organic Chemistry.
In synergistic collaborations between researchers from both universities in Innsbruck, the new FT-ICR instrument will be used in an interdisciplinary way to study RNA structure, modification, reactivity/catalysis, and interactions with proteins, small molecules and inorganic ions that form the molecular basis of regulatory processes in cells. The novel insights will provide fresh impetus for the development of RNA drugs and therapeutics (RNA vaccines, antisense RNA, siRNAs, etc.) to combat human diseases caused, for example, by viral pathogens, and open the door to collaborations with research departments

CMBI SPECIALS – Research programs and infrastructure funding

from the public sector and the pharmaceutical industry. In addition, the infrastructure will add significant value to the education of students who are in high demand as key personnel in the chemical, pharmaceutical, and biotechnology industries. The new instrument is financed by the FFG's R&D Infrastructure Funding 2023 with co-financing from the European Union and the University of Innsbruck and has been installed end of 2024.

>> FWF FUNDED RESEARCH GROUP – MECHANISMS OF CELLULAR SENESCENCE



www.senioprom.com

Aging is a complex process driving the progressive functional decline of various tissues. The FWF research group "SENIOPROM", coordinated by Pidder Jansen-Dürr (CMBI), aims to better understand the molecular mechanisms that contribute to cell aging, also known as cellular senescence. In mammals, including humans, senescent cells accumulate during aging, compromise organs' function, and contribute to various age-related diseases. In the SENIOPROM project (started in March 2023), the team aims to elucidate how the interplay of mitochondria with other organelles, new mechanisms of metabolic regulation, and the maintenance of functional proteins contribute to cell senescence. Based on these subcellular processes, we aim to develop and characterize new small molecules that selectively remove senescent cells or render them harmless. We utilize cell cultures, different model organisms, and simplified artificial human organs to investigate mechanisms and test potential new treatment strategies. SENIOPROM generates added value through the interdisciplinary collaboration between molecular and cell biology, biotechnology, pharmacology, and computational and medicinal chemistry. The consortium involves two CMBI members Pidder Jansen-Dürr (coordinator) and Teresa Kaserer, as well as Corina Madreiter-Sokolowski (University of Graz) and Markus Schosserer (Medical University of Vienna). Further information can be found at www.senioprom.com.

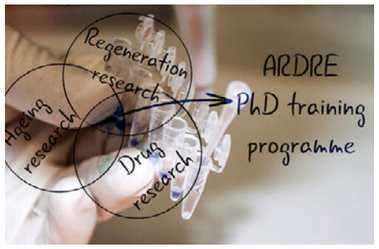
>> ERC CONSOLIDATOR GRANT – 'CRAFTMOL' (2021–2027)

Thomas Magauer (CMBI) is a "molecular architect" with a passion and enthusiasm for highly functionalized, bioactive molecules. Since his time as a doctoral student, he has been fascinated by the complexity and diversity of molecular architectures, molecules, and their role as valuable lead structures for the development of novel drugs. For the

https://www.uibk.ac.at/organic/magauer/index.html.en

systematic investigation of these molecular architectures, considerable amounts of substance must be available. "However, many of the architectures are currently not accessible from natural sources or require lengthy and expensive synthesis strategies. The CRAFTMOL project was developed to provide a solution to this problem. Together with a team of vivid international master students, PhD students and postdocs, novel polyene cyclizations are being investigated in order to construct currently inaccessible natural substances with, for example, cancer-inhibiting, antiviral or anti-inflammatory effects", explains Magauer. Chemists recognized the potential of this cyclization for organic synthesis early on and went to great lengths to emulate it in the chemical laboratory. In the CRAFTMOL project, novel modes for polyene cyclizations and novel termination steps are developed. Based on the two complementary, synergistic work packages, the limitations of previous systems are circumvented and the synthesis of biologically active molecules is simplified.

>> Marie Curie CoFund PhD program "ARDRE" – Ageing, Regeneration and Drug Research (2020–2025)



www.uibk.ac.at/projects/dp-ardre

Twelve internationally recruited young researchers start their four-year projects. Coordinated by Pidder Jansen-Dürr and his deputies Kathrin Thedieck and Frank Edenhofer, the major aims of this program are to uncover cellular and molecular mechanisms acting in organismic aging and regeneration, and to use the new findings in developing strategies for producing novel drugs. Building upon an earlier University of Innsbruck PhD program, AGEREG, which had been established within the frame of the CMBI, twelve research groups from across all of the major CMBI areas, biology, chemistry, and pharmaceutical sciences, participated in the competitive ARDRE application process. The European H2020 program granted the application and provided a total of 1.3 Million Euro. In addition, a corresponding amount of money is granted by the University of Innsbruck. Taking the PhD candidates from ARDRE and AGEREG together, currently more than 25 young researchers work on topics of stem cells, ageing, regeneration and drug design, making this research area one of the major educational strongholds among the Tyrolean life sciences.
Core element of the two programs is their interdisciplinary nature, strongly aiming at collaborations between the participating groups.

CMBI SPECIALS – Research programs and infrastructure funding

This is supported by a specific educational schedule, in which ARDRE PhD students participate in research group seminars and special lectures, lab courses and regular retreats to discuss current progress. The program also offers and supports international mobility to mediate collaboration with defined academic and industrial partner institutions across the world. At the end of the four-year tenure, ARDRE should result in strongly trained PhDs with a unique knowledge about modern applications and trends in ageing and regeneration research, and with a basic understanding of drug discovery.

>> SFB CONFERENCE *RNA-DECO* in Innsbruck

https://www.uibk.ac.at/de/newsroom/2024/sfb-tagung-in-innsbruck/
https://www.rna-deco.org/

The members of the FWF Special Research Area RNA-DECO met in Innsbruck at the end of January 2024. Funding for the Austria-wide research network was extended for another four years. The network's research teams focus on ribonucleic acid (RNA), which plays a decisive role in the conversion of genetic information into proteins. In addition, special types of RNA fulfill numerous other tasks in the cell. The building blocks of these biomolecules are often chemically modified, which influences their function. Around 150 such modifications are known to date. The research groups in Vienna and Innsbruck are investigating the extent and type of these changes and their biological consequences as part of the special research area.
In the second funding period, the research network will expand its focus on understanding the structural implications of RNA modifications and their recognition by cellular stress and immune sensor factors. To achieve this, the network led by Michael Jantsch from the Medical University of Vienna has been expanded to include structural chemist Christoph Kreutz from the University of Innsbruck and molecular microbiologist Isabella Moll from Perutz Labs Vienna. In addition to Kreutz, Ronald Micura from the Institute of Organic Chemistry is also involved as a proven expert in the field of chemical synthesis of RNA. He is contributing this know-how to the development of tools for the artificial modification of RNA and its labeling. The groups led by Alexandra Lusser and Matthias Erlacher from the Medical University of Innsbruck are also part of the network (https://www.rna-deco.org/).

CMBI SPECIALS – Publication highlights

>> GOOD THINGS TAKE TIME

https://www.uibk.ac.at/de/newsroom/2022/gut-ding-braucht-weile/

The ERC project HALODRUGSYN has achieved another major success: Under the guidance of Thomas Magauer (CMBI) from the Institute of Organic Chemistry, Jan Paciorek, Denis Höfler and Kevin Sokol succeeded in the world's first chemical synthesis of the DOSI natural product psammaplysin A 40 years after its discovery. Their work was published in the *Journal of the American Chemical Society* (144, 19704–19708, 2022).
Dihydrooxepin-spiroisoxazoline (DOSI) natural products are a structurally unique family of marine natural products. The psammaplysin subfamily contains more than 35 members and exhibits a variety of biological activities, including potent antiproliferative, antiviral and antibiotic effects. Psammaplysin A was the first member to be isolated from the marine sponge Psammaplysilla purpurea 40 years ago, but its unique molecular structure was only fully elucidated 30 years later.
Initial attempts to produce the fascinating natural substance in the laboratory failed due to the unusually sensitive decoration of the spirocyclic backbone. "It is now known that the backbone is decisive for the pharmaceutical activity and that the attached dibromotyrosine side chain plays a crucial role in modulating the biological activity," says Thomas Magauer from the Institute of Organic Chemistry. After five years of intensive work, his research group was able to overcome all obstacles and realize the world's first synthetic access to psammaplysin A. "An early ring extension to build up the spirocyclic backbone and the sequential functionalization carried out at the end of the synthesis were decisive for the success," says Magauer. The highly efficient and flexible synthesis proceeds from commercially available starting materials via 13 steps to the natural product and also opens up the possibility of specifically producing novel derivatives and establishing a previously inaccessible substance library.

>> HOPE FOR UNIVERSAL FLU VACCINE

The CMBI researchers Klaus Liedl and Monica Fernández-Quintero were part of a research consortium that, together with colleagues from the University of Chicago, the Scripps Research Institute and the Icahn School of Medicine, identified a new class of broadly neutralizing antibodies against the influenza virus and thus made important progress in the search for a universal flu vaccine. They published their findings in *Nature* (602, 314–320, 2022).
Vaccines against the flu virus usually trigger the immune system to produce antibodies that recognize the head of the hemagglutinin (HA), a protein that extends outward from the surface of the virus. The head

CMBI SPECIALS – Publication highlights

https://www.uibk.ac.at/de/newsroom/2022/neueste-ergebnisse-lassen-auf-universellen-grippeimpfstoff-hoffe/

is the most accessible area of the HA and therefore a good target for the immune system; unfortunately, it is also one of the most variable: from year to year, the HA head frequently mutates, so that adapted vaccines against the flu virus are required each year. The researchers have developed experimental flu vaccines that are more universal and stimulate the body to produce antibodies against the less variable stalk region of HA, which extends like a stalk between the influenza virus and the HA head. Some of these universal flu vaccines are currently in early clinical trials. In the study, different antibodies were analyzed in the blood of people who had either received a seasonal flu vaccine, participated in a phase I trial for an experimental universal flu vaccine or had contracted the flu naturally. Many of the antibodies present in the participants' blood were antibodies that were already known to recognize either the HA head or the HA stalk. However, one group of new antibodies stood out: these antibodies bind to the lower part of the stalk, which the scientists subsequently referred to as the anchor. This anchor is located near the site where each HA molecule is attached to the membrane of the influenza virus. In total, the scientists identified 50 different antibodies against the HA anchor, which came from a total of 21 people.

"Our contribution to this international collaboration was the simulation and optimization of antibody models. Building on our many years of work in this field, we are able to simulate antibodies and their behavior using graphics processing units (GPU). As we assemble our computer systems ourselves, we can adapt them to particularly challenging problems," explains Klaus Liedl.

Andrew Ward and his colleagues at Scripps Research then examined the antibodies using cryo-electron microscopy (cryo-EM) and found that the results obtained in the laboratory confirmed the results of the initial simulations. "Once the reliability of our simulations had been confirmed, we used further models to investigate four antibodies and were thus able to provide significant insights into their behavior and binding properties," adds Monica Fernández-Quintero. "These models also confirmed that the newly identified type of antibody is highly conserved in both structure and function. This has also made it immensely easier for us to compare these structures, because if they are all relatively the same, the dynamics and differences can be specifically localized and studied in more detail," says the young scientist.

>> NEWLY DISCOVERED LIPID PREVENTS CELL DEATH

https://www.uibk.ac.at/de/newsroom/2022/neu-entdecktes-lipid-stoppt-den-zelltod/

Stress responses are a double-edged sword and must be kept in balance to be beneficial to the body. That is why cells also contain substances that stop stress reactions and inhibit cell death. An international consortium of research groups led by the CMBI researcher Andreas Koeberle has been able to prove that a membrane lipid called PI(18:1/18:1) is significantly involved in this process. The study, published in the research journal *Nature Communications* (13, 2982, 2022) opens up many interesting medical possibilities.

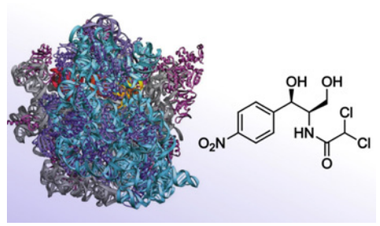
The regulation of stress reactions involves many different enzymes. One of them is the enzyme SCD1. It converts saturated fatty acids into unsaturated ones and is therefore particularly effective against stress that is triggered by fats in harmful concentrations.

In principle, this process benefits the organism's health. However, it can become dangerous if carried out excessively. Researchers have long seen a clear connection between SCD1 and inflammation, metabolic diseases and cancer. The full functional scope of this enzyme is still unknown. As a consequence, treatments that specifically inhibit SCD1 can lead to severe side effects and are not approved for therapy.

Researchers have now been able to trace the stress response-inhibiting effect of SCD1 back to an indirect product of this enzyme: The membrane lipid PI(18:1/18:1), which is largely composed of a fatty acid produced by SCD1. "What is particularly interesting is that stress-associated processes, such as the ageing process, resistance to chemotherapy or the development of tumors all influence the amount of PI(18:1/18:1) in the affected tissues. There is a clear connection that opens up new therapeutic approaches," says Andreas Koeberle. "We have deciphered a very fundamental process with this study. It's a significant starting point and sets new directions for further research," he adds.

Andreas Köberle was Professor at the University of Innsbruck until 2024, when he accepted an offer to become Professor of Molecular and Chemical Cell Biology at the University of Graz.

>> MOLECULAR MECHANISM OF ANTIBIOTIC ACTION ELUCIDATED



https://www.uibk.ac.at/en/newsroom/2022/antibiotikum-molekularer-wirkmechanismus-aufgeklart/

Researchers from the CMBI and the University of Illinois at Chicago have been able to elucidate the molecular mechanism of action of the antibiotics chloramphenicol and linezolid and published their findings in the journal *Nature Structural & Molecular Biology* (29, 152-161, 2022). Antibiotics targeting the cellular protein factories – the ribosomes – serve as powerful antimicrobial agents. They are also important tools to study the ribosomal catalytic center targeted by many drugs. The classical antibiotic chloramphenicol (CHL) and the newest clinically significant linezolid (LZD) have long been considered arbitrary inhibitors of protein synthesis, causing delays at the ribosome for each codon of each gene that is translated. However, recent discoveries have shown that CHL and LZD preferentially arrest translation when the ribosome

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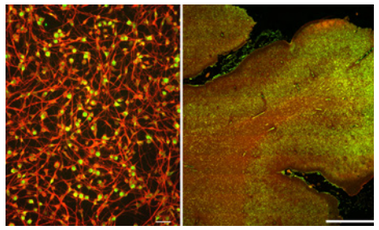
needs to synthesize specific amino acid sequences. The molecular mechanisms underlying this context-specific action of ribosome inhibitors are unknown. The research groups of Yury Polikanov in Chicago and Ronald Micura from the Institute of Organic Chemistry at the University of Innsbruck now present high-resolution structures of ribosomal complexes with or without CHL that carry specific nascent peptides that support or even abolish the drug effect. Their data demonstrate that the penultimate amino acid of the resulting peptide directly modulates the affinity of the antibiotic to the ribosome. Specific interactions of the side chain of alanine, threonine or serine with the drug strengthen it, while the side chains of all other amino acids hinder its correct placement at the binding site.

The chemical basis for the success of the study was provided by Ronald Micura's research group with the solid-phase synthesis methods they developed. This chemistry allows the complete construction of artificial peptidyl-tRNA molecules that resemble the natural systems on the ribosome, but are much more stable, enabling structural biology studies.

>> ALZHEIMER: CANCER DRUGS AS A NEW TREATMENT APPROACH



https://www.uibk.ac.at/de/newsroom/2022/alzheimer-krebsmedikamente-als-neuer-behandlungsansatz/

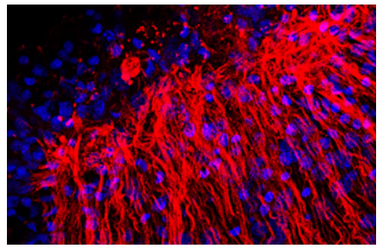
Alzheimer's nerve cells undergo the same change in their metabolism as cancer cells - this has been demonstrated by molecular biologists led by Jerome Mertens at the CMBI. The scientists published this important step for the development of possible treatment methods in the journal *Cell Metabolism* (34, P1248-12663.E6, 2022).

The causes of sporadic Alzheimer's disease are even more of a mystery compared to the better-researched, genetically determined, hereditary form of the disease. Jerome Mertens' team at the Neural Aging Laboratory at the Institute of Molecular Biology at the University of Innsbruck is using induced neurons (iNs) - nerve cells that are grown from patients' skin cells and contain the patient's age and all other epigenetic data - to gain a better understanding of the disease.

Mertens' team, in collaboration with scientists from the Salk Institute and the University of Denver, were able to confirm that Alzheimer's neurons undergo the same change in their metabolism as cancer cells. "Our previous studies have already shown that Alzheimer's neurons are very similar to cancer cells - with the major difference that cancer cells grow uncontrollably and Alzheimer's neurons die uncontrollably," explains Larissa Traxler, the first author of the study. "We therefore focused specifically on the metabolism of Alzheimer's neurons and compared it with the very specific and well-researched metabolism of cancer cells." These investigations confirmed the similarity: the so-called Warburg effect - a change in the metabolism of cancer cells from the adult to the embryonic stage - also occurs in Alzheimer's nerve cells. "Alzheimer's neurons undergo a very similar switch to embryonic metabolism as cancer cells. However, since cell death is initiated in nerve cells as soon as they begin to divide, they die in contrast to cancer cells, which multiply uncontrollably," explains Traxler.

In cancer therapy, there are already active substances that specifically target this Warburg effect. In particular, the protein pyruvate kinase M2 (PKM2) is targeted. PKM2 is increasingly produced in cancer cells, but also in Alzheimer's neurons, and is considered one of the main regulators in the switch to embryonic metabolism. "We tested in cell experiments whether these PKM2 modulators also work in Alzheimer's neurons. Fortunately, we were able to show that the active substances that inhibit the Warburg effect in cancer cells also lead to the nerve cells retaining their adult stage for longer in Alzheimer's nerve cells," explains Larissa Traxler. In the next step, the molecular biologists now want to work on optimizing these active substances for ageing nerve cells and modifying them so that they can optimally reach the brain and act against Alzheimer's disease there.

>> HIPPO AND THE HYDRA



https://www.uibk.ac.at/de/newsroom/2022/hippo-und-die-hydra/

The body structure of the vast majority of animals is based on an axis that runs from the head to the torso. A major question in developmental biology is how the cells of the first multicellular animals organized themselves and how this body axis was formed. A new study published in the journal *Proceedings of the National Academy of Sciences* (119, e2203257119, 2022) shows that the evolutionary origins of the body axis lie in the so-called Hippo signaling pathway. The CMBI member Bert Hobmayer and his research group at the Institute of Zoology played a key role in the research and provided important data.

Signaling pathways are molecular biological processes that serve communication between cells. Through the formation and exchange of certain molecules, cells can absorb, process and react to information from the environment or the body. The Hippo signaling pathway has an important function in higher animals, such as mammals and birds. It controls cell division in the developing organs and ensures that they assume their correct size and three-dimensional shape. If the Hippo signaling pathway is defective, tissue thickening can occur, similar to the skin of a hippopotamus - hence the name.

Researchers at the Lunenfeld-Tanenbaum Research Institute in Toronto and the Washington University School of Medicine, with support from the Institute of Zoology at the University of Innsbruck, have described the function of this signaling pathway for the first time in evolutionarily ancient animals. The Hippo signaling pathway probably originated in such animals. The researchers studied the freshwater polyp Hydra. Bert Hobmayer's team at the Institute of Zoology has been working intensively on this model organism for years. Using electron microscopy, they investigated the complex mechanism and provided important data on the internal organization of the cells that are controlled by the Hippo signaling pathway. "Hippo is a complex mechanism that is not yet fully

CMBI SPECIALS – Publication highlights

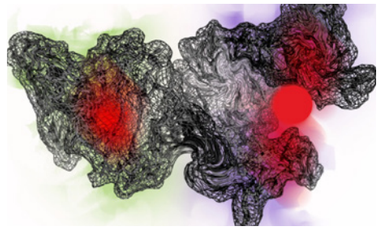
understood in developmental biology," says Hobmayer. "We have now found similar principles of action in the simply built hydras, but they affect the entire animal."
The Hydra is a simple animal that is considered practically immortal. It constantly renews its tissue, can completely replace entire body parts or form an entire new organism from individual cells. It also reproduces asexually by forming a bud from its body, which then grows into a new clone. With each new bud, a new body axis is created. The research results show that the Hippo signaling pathway influences the cell division rate in the entire hydra. It therefore also controls the development of new animals. In addition to controlling tissue growth and asexual reproduction, the Hippo signaling pathway also produces signaling molecules that are necessary for the development of a normally formed body axis. This means that the researchers have not only come a big step closer to understanding the development of an important signaling pathway. The new knowledge about the simply built hydra also opens the door to further studies with this model organism.

>> NATURAL SUBSTANCE SYNTHESIZED FROM CORAL

https://www.uibk.ac.at/de/newsroom/2023/naturstoff-aus-korallen-synthetisiert/

Chemists led by Thomas Magauer at the CMBI have succeeded in synthesizing the natural substance waixenicin A for the first time. This is found in soft corals and is of great interest to the pharmaceutical industry due to its potential medical applications.
Soft corals are a rich source of bioactive natural substances. The genus *Xenia* produces the so-called *Xenia* diterpenoids, which are characterized by the great diversity of their chemical structure and biological activity. Due to their promising biological properties, pharmaceutical companies are also increasingly interested in them - some *xenia* diterpenoids have shown anti-inflammatory and anti-cancer effects, among other things. The first representatives of these substances were isolated as early as 1977, but they have so far only been studied to a limited extent.
The biggest challenge is the poor availability of natural sources. Many marine organisms, including corals, cannot be cultivated for the most part. Large-scale extraction of Xenia diterpenoids from corals in nature would represent an enormous intervention in their sensitive ecosystem. Several attempts to produce the complex molecular structures in the laboratory have failed and to date only a handful of successful syntheses have been described in the literature.
Magauer's team finally succeeded in producing waixenicin A in the laboratory in 2023 and published the story in *Journal of the American Chemical Society* (145, 11811–11817, 2023). The synthesis was very challenging due to the special properties of the natural product, but was ultimately successful with the help of an efficient synthesis strategy that Magauer's group had developed in previous work in the field of herbicide synthesis.
Despite early progress and a first important breakthrough in 2017, the chemists were initially unable to access the desired bicyclic scaffold. The presence of labile functional groups and a strained nine-membered ring prevented a successful synthesis for several years. The solution was finally provided by an earlier study on the production of the herbicide cornexistin. A highly efficient intramolecular ring closure for the assembly of the scaffold could be derived from this older work. A sequential functionalization of a bicyclic key intermediate enabled the selective incorporation of the side chain and opened up the synthesis of waixenicin A for the first time. Further diversification of the key intermediate allowed access to two additional xenia diterpenoids: Particularly fascinating was the conversion to xeniafaraunol A, which could be carried out in a single step. The significance of this step for biosynthesis and biological activity has not yet been investigated, so exciting questions are guaranteed.

>> ELUCIDATING RNA-DRUG INTERACTIONS



https://www.uibk.ac.at/de/newsroom/2023/rna-wirkstoff-wechselwirkungen/

How small chemical compounds interact with RNA and affect RNA-mediated gene regulation is of great interest for the development of potential therapeutics. Chemists led by the CMBI member Kathrin Breuker have now used a novel mass spectrometric method to shed light on the binding mode of the aminoglycoside Neomycin B to an mRNA riboswitch. Their study was published in the *Journal of the American Chemical Society* (145, 15284–15294, 2023).
In cellular processes, ribonucleic acids (RNA) specifically recognize proteins and/or small organic molecules. Understanding these binding processes in detail is important for advancing the development of potential therapeutics that target RNA. One challenge in studying RNA complexes with small molecules (and potential drugs) is that RNA can provide multiple binding motifs that are difficult or impossible to resolve using conventional methods.
For their study, Kathrin Breuker's team used a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer, which allows RNA complexes of different stoichiometries to be separated from each other in the gas phase and studied individually. "For the RNA sequence with the highest regulatory factor for riboswitch function, we identified two different binding motifs for Neomycin B and were also able to determine their relative populations," Kathrin Breuker recounts. "By introducing RNA base mutations, we were able to specifically shift the populations of the two binding motifs and thus develop a better understanding of aminoglycoside binding to the riboswitch." As the populations of the two binding motifs were the same for the non-mutated sequence, the Innsbruck researchers suggest that riboswitch function is controlled by the simultaneous binding of two Neomycin B

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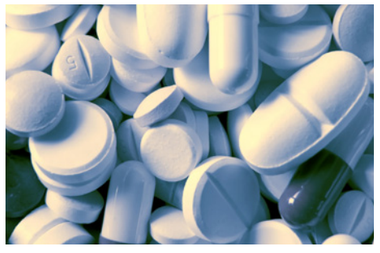
molecules. The new experimental approach allows systematic studies of the binding specificity of RNA and, complementary to established methods for structure elucidation, will provide new insights into RNA function at the molecular level.

>> NEXT-GENERATION ANALGESICS WITH LESS ADVERSE EFFECTS



https://www.uibk.ac.at/de/newsroom/2023/schmerztherapeutika-der-nachsten-generation/

Pain is still an unsolved medical condition, and it is among the most prevalent and debilitating human illnesses. Chronic pain conditions are still poorly managed because of the lack of efficacious therapies and high side effects burden. Opioids continue to comprise the most important class of painkillers. Opioid prescription drugs that are frequently used in pain medication can lead to drug dependence with serious consequences, including respiratory depression, which is potentially lethal, in particular when the opioid is overdosed. Medical use and misuse of opioids have significantly increased in the last decades, leading to an opioid epidemic worldwide. In recent years the hunt for safer alternatives has been the focus in drug discovery.

The group of Mariana Spetea (CMBI) is a part of an international team of scientists from the Medical University of Vienna, University of Vienna, University of Queensland, University of Oregon, University of Maryland Baltimore, University of Washington and Washington University School of Medicine. Applying a computer-assisted workflow an opioid-like molecule acting on the kappa-opioid receptor has been developed, which effectively alleviates experimental pain but with fewer undesirable side effects. The "de novo" design process offers an enormous improvement over existing drug discovery methods commonly used in pharmaceutical research, such as structure-based virtual library or molecule-based high-throughput screenings. Since the kappa-opioid receptor is a prototypical GPCR, the method may be applied, in the future, for the development of better drugs and drug therapies with reduced side effects for other GPCRs. The study was published in *Nature Communications* (14, 8064, 2023).

>> MORTAL AMONG IMMORTALS

https://www.uibk.ac.at/de/newsroom/2023/sterblich-unter-unsterblichen/

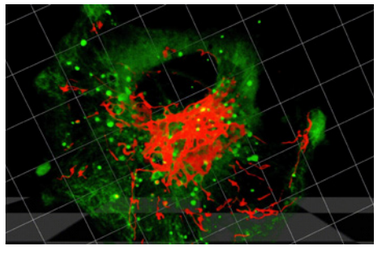
At first glance, the hydra is an inconspicuous animal. Several tentacles sit at the end of an elongated body just a few millimetres long. What makes them so interesting for researchers is that they are practically immortal and free from tumor formation. Hydras constantly renew their tissue, can regrow body parts or form an entire organism from individual cells. The CMBI research groups of Bert Hobmayer and Peter Ladurner have been researching these organisms for a long time, most recently describing the development of their body axis and the differentiation pathway of their stem cells. The team has now been able to determine and analyze the entire genetic information of Hydra oligactis using the latest DNA sequencing technology, Oxford Nanopore Sequencing. This was the last hydra species whose genome was not yet fully known. The results are so interesting because Hydra oligactis, unlike all other hydra species, can form tumors and die.

"The hydra we examined comes from Lake Piburger See in Tyrol," explains Bert Hobmayer. "For our analysis, we selected a specimen that showed particularly strong signs of stress-induced ageing. This animal was clonally amplified in the laboratory. Now that we know the Hydra oligactis genome in detail, we can investigate much more precisely how individual genes contribute to stress-induced cellular ageing in these animals. We can then study these molecular processes comparatively in other species whose cells do not age and do not die." The Innsbruck researchers' work was part of an international project led by Celina Juliano at the University of California in Davis, the results of which were published in the journal *Genome Research* (33, 283–298, 2023).

The stem cells of the freshwater polyp have already been studied in detail and provide valuable information on how tissue cells differentiate from stem cells. However, little was previously known about the genetic mechanisms by which these stem cells maintain and differentiate. The research team has now fundamentally expanded our knowledge of the genetic structure of various hydra species. In addition to Hydra oligactis, the genome of another hydra species was sequenced, the gene activation of individual cells was examined and cataloged, and the entire epigenome of Hydra was analyzed. The epigenome refers to chemical markings and modifications to the DNA, which can also occur due to environmental factors. These influence which genes are read out more frequently and which less frequently. The epigenome therefore has a major impact on the development of cells and diseases such as cancer. The data obtained forms an important basis for further research into stem cells, regeneration and the ageing of hydrons.

CMBI SPECIALS – Publication highlights

>> MOLECULAR MECHANISM OF SKIN AGEING ELUCIDATED



https://www.uibk.ac.at/de/newsroom/2024/molekularer-mechanismus-der-hautalterung-aufgeklart/

A team of scientists led by Pidder Jansen-Dürr (CMBI) and Maria Cavinato at the Institute for Ageing Research is dedicated to researching the connection between environmental influences and skin ageing processes at a molecular level. In a study recently published in the journal *Aging Cell* (23, e14186, 2024) they used cell cultures to explicitly investigate the influence of ultraviolet radiation on the molecular mechanisms in the mitochondria of skin cells.

"Mitochondria, the so-called 'power plants of the cell', are damaged by UV radiation," explains first author Maria Cavinato. "This damage triggers a mechanism of mitochondrial quality control known as mitophagy." Through mitophagy, damaged mitochondria are broken down into their components by inclusion in digestive vesicles - so-called autophagolysosomes - which can be used to build new mitochondria. This cellular recycling program is of crucial importance for the health status of our cells.

"The problem is that we are exposed to UV radiation not just once, but very frequently. Sunlight damages the mitochondria with every exposure and, once a certain amount is reached, the cells are no longer able to save the damaged mitochondria. In this case, the cells become senescent," explains Maria Cavinato. Senescent cells stop dividing, but do not die, but remain in the tissue. There they damage the skin structure and drive the extrinsic ageing process of the skin, also known as photoaging. To protect the tissue from extrinsic ageing, one possible solution to the problem would be to remove cells on their way to senescence by blocking mitophagy, but such procedures have not yet been established. "In the study, we are investigating a specific form of mitophagy in which the protein NIX is significantly involved," explains Maria Cavinato. NIX recognizes the damaged mitochondrion in UV-treated cells and connects it to an autophagosome, whose fusion with a lysosome creates the autophagolysosome in which the mitochondrion is recycled. "If NIX expression is blocked by genetically manipulating the cells, mitophagy is prevented and the cells do not become senescent in the first place, but die because they are dependent on mitophagy to repair the mitochondria on the way to senescence," explains Pidder Jansen-Dürr.

The results of the long-term study show for the first time that NIX is a key mitophagy receptor in the process of UV-induced senescence in skin cells. The new findings on the mechanisms of mitophagy indicate that diseases triggered by high exposure to solar radiation are due to senescent cells remaining in the tissue after UV treatment. In future, this could lead to new treatment methods that prevent the development of senescent cells in the skin by pharmacologically blocking mitophagy and that could attenuate or prevent skin ageing processes such as photoaging.

>> DIABETES AND GENDER

https://www.uibk.ac.at/de/newsroom/2024/diabetes-und-geschlecht/

Men develop type 2 diabetes more often than women. The CMBI member Petronel Tuluc from the Institute of Pharmacy found a possible explanation for this in the different electrical activity of beta cells in the pancreas of male and female mice.

Diabetes has long since become a disease of pandemic proportions: According to WHO statistics, there were 537 million diabetics in 2021, and the trend is rising. Diabetes is the ninth most common cause of death worldwide. The underlying biology and causes are generally well researched. However, why women have a lower risk of diabetes than men has not yet been sufficiently clarified. The reasons for this are explained by Petronel Tuluc, who recently published exciting news on gender-specific differences in diabetes with his research group. "Historically, diabetes research was mainly carried out on male mice. Fortunately, this has now changed and is also reflected in national and international funding guidelines," says the scientist. In a study on healthy female and male mice, he focused on a very specific aspect of glucose metabolism: the electrophysiological properties of beta cells. These specialized cells in the pancreas are crucial for maintaining normal blood glucose levels because they are responsible for the production and release of insulin. Insulin is the only hormone that can lower our blood sugar levels by promoting the transport of sugar from the blood into the cells. "We looked at what happens in female and male beta cells when the glucose concentration is increased above 5 millimoles," says Tuluc, explaining the experiment in which he and Noelia Jacobo-Piqueras discovered numerous noteworthy differences in the way beta cells function. In their publication in *The Journal of Clinical Investigation Insight* (9, e171609, 2024) first author Noelia Jacobo-Piqueras and her mentor Petronel Tuluc focus on the differences they observed in the functioning of potassium channels in beta cells: At the same high glucose concentration, female beta cells leak less potassium than male beta cells. "These reduced potassium currents lead to higher electrical activity, which in turn results in higher insulin production and release in female beta cells," the scientist explains succinctly. The higher electrical activity and electrical potential in the cell membrane also reduces the influx of another substance, namely calcium, into the cells, which is why female beta cells live longer.

This complex mechanism and its gender-specific differences could have far-reaching implications for the treatment of diabetes. Tuluc urges caution, as these are findings from the mouse model that cannot be easily transferred to human cells. Nevertheless, he assumes that the findings, which still need to be verified in humans, open up new possibilities. "If we can find ways to modulate the potassium channel, innovative treatment approaches may emerge."

Tuluc's aim is to find out in follow-up studies what regulates the potassium channel in detail. "We were able to observe the mechanism. Now we have to take a step back and clarify the causes. Then we can try to reproduce the data in humans," explains the scientist. He is well aware that this is a challenging undertaking. "Sex hormones function in an extremely complex way - you can see differences between the sexes in many cell functions and tissues, such as the cardiomyocytes in the heart or the smooth muscles in the blood vessels. However, the question is always how relevant these

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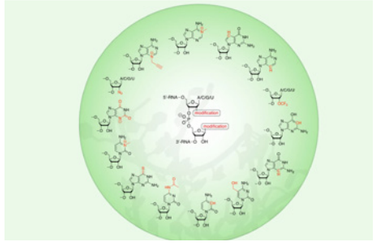
differences are and how we can use this knowledge to develop better or patient-oriented drug therapies. This will not be easy, but I am confident that research can meet this challenge with the current progress," adds Petronel Tuluc, who is venturing into the unknown with his 'Molecular Endocrinology' research group.

>> BUILDING RNA MOLECULES



https://www.uibk.ac.at/de/newsroom/2024/rna-molekule-bauen/

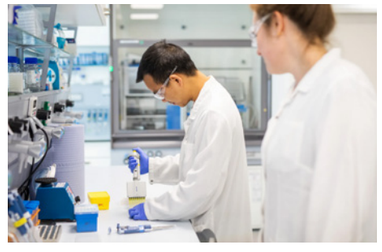
Ribonucleic acid plays a central role in basic research, biotechnology and biomedicine. Ronald Micura's team at CMBI is one of the leading groups in the chemical synthesis of RNA. In a review article in *Angewandte Chemie International Edition* (63, e202403063, 2024) they discuss the latest developments in this field.

The importance of RNA stems not only from its function as a mediator between DNA and proteins, but also from its role in gene regulation, developmental biology and disease. Many properties of RNA are based on its ability to undergo chemical modifications that affect its stability and function. In basic research, RNA is a valuable tool for studying and understanding cellular mechanisms and molecular signaling pathways. In medicine, RNA is used for vaccination and therapeutic approaches. RNA-based vaccines, such as those against the coronaviruses, exploit the ability of the molecule to encode antigenic proteins and thus trigger immune responses against pathogens. RNA therapeutics also offer a targeted approach to treating disease by modulating gene expression.

In the laboratory, RNA is usually produced by in vitro transcription (IVT), where it is made from DNA templates using RNA polymerases. IVT is the method of choice, especially for long RNAs (>200 nucleotides) in particular. For short RNAs (<100 nucleotides), chemical synthesis has become established as a precise method for the production of RNA sequences and structures, allowing the site-specific incorporation of natural or artificial modifications. Micura's team at the Institute of Organic Chemistry has become one of the world's leading research groups in the field of chemical RNA synthesis and is part of the FWF funded special research area *RNA Deco* (https://www.rna-deco.org/).

In the review article, they discuss recent developments in the field, starting with new protection concepts as part of ongoing efforts to overcome current size limitations. They continue with selected modifications that pose a major challenge for their incorporation into RNA. These include deazapurine nucleosides, which are required for atomic mutagenesis to elucidate mechanistic aspects of catalytic RNA, and RNA containing xanthosine, acetylcytidine, 5-hydroxymethylcytidine, 3-methylcytidine, 2'-trifluoromethoxy and 2'-azido ribose modifications. Recent advances in the pure chemical synthesis of 5'-capped mRNAs and the enzymatic ligation of chemically synthesized oligoribonucleotides to obtain long RNA with several different modifications, as required for single-molecule fluorescence (FRET) studies, are also presented. Finally, the authors show promising developments in RNA-catalyzed RNA modification using cofactors that confer bioorthogonal functionalities.

>> INTERVENTION IN FAT METABOLISM PROMISES CANCER TREATMENT OPTIONS



https://www.uibk.ac.at/de/newsroom/2024/neue-behand-lungsmoglichkeiten-bei-therapieresistentem-krebs/

Metastatic cancer is only completely curable in rare cases. Although the progression of the disease can be slowed down medically, cancer cells often develop resistance to chemotherapeutic agents. This makes them particularly insidious and deadly. A new study by the University of Innsbruck, the University of Erlangen-Nuremberg, the University of Würzburg and the Massachusetts Institute of Technology, which was recently published in the journal *Nature Cell Biology* (26, 1470–1481, 2024), explains how it might be possible to treat cancer in the future despite resistance to therapy.

'The basis of our research work is a cellular transformation process known as epithelial-mesenchymal transition (EMT),' explains CMBI scientist Andreas Koeberle. The prerequisite for this process is that individual epithelial cancer cells, which make up a compact tumour, transform into cancer cells with mesenchymal properties. Such cancer cells detach from the original tumor, can migrate through the body and form metastases in a wide variety of places. 'They are often also more resistant to conventional chemotherapeutic agents,' says Koeberle.

In the course of their metamorphosis, mesenchymal cells change their metabolism and increasingly incorporate polyunsaturated fatty acids into their cell membrane instead of monounsaturated fatty acids. Fats give the cells structure, but also make them more susceptible to a mechanism that was only discovered in 2012 and is still not fully understood: ferroptosis. 'Ferroptosis is a non-programmed cell death mediated by iron and oxygen radicals, which is also associated with neurological and other degenerative diseases,' explains study author Thomas Brabletz from the University of Erlangen-Nuremberg. 'The fatty acids oxidize, damage the cell membrane and ultimately destroy the entire cell.'

In laboratory experiments, researchers have already succeeded in specifically killing mesenchymal tumor cells by exploiting their ferroptosis sensitivity. 'The pharmacological manipulation of certain enzymes of fat metabolism can lead to increased storage of polyunsaturated fatty acids in the cell membrane, even in cancer cells that have already built up a certain resistance to ferroptosis. This further increases their ferroptosis sensitivity,' concludes Koeberle.

The study lays the first foundations for the development of new active substances against aggressive types of cancer with a high metastatic potential other than classic chemotherapeutic agents. However, because the epithelial cells of the original tumor do not respond to ferroptosis due to their low concentration of polyunsaturated fatty acids, a combination of these active substances with classic chemo- and immunotherapies is planned for cancer treatment in the long term.

Andreas Koeberle was Professor at the University of Innsbruck until 2024, when he accepted an offer to become Professor of Molecular and Chemical Cell Biology at the University of Graz.

Native top-down MS for the study of small molecule binding to RNA

Kathrin Breuker

>> Department of Organic Chemistry

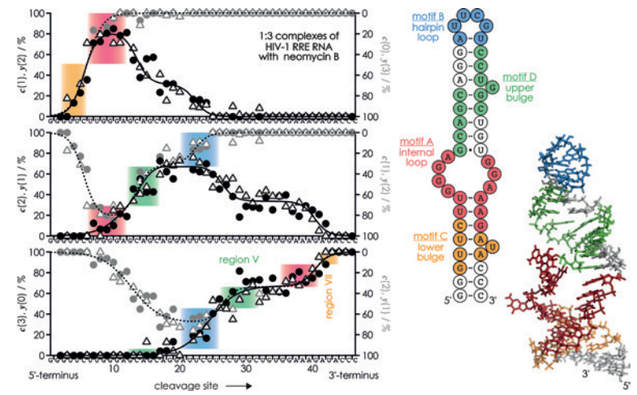
>> Goal: The current focus of our research is to contribute to a better understanding of the interactions of small molecules, including potential therapeutics, with ribonucleic acids (RNA) using native top-down mass spectrometry (MS).

>> Background: Mass spectrometry of RNA is emerging as a thriving field of research with applications in chemical and structural biology, the development of RNA-targeting drugs, and modification analysis of biologically relevant or therapeutic RNA. Based on fundamental insights from mechanistic studies in the gas phase, we are developing and applying new approaches for RNA and RNA complex characterization by high-resolution top-down mass spectrometry using a Fourier transform ion cyclotron resonance (FT-ICR) instrument.

>> Research highlights and outlook: RNA is a promising target for drug development, but progress in this field is critically limited by a limited understanding of RNA-small molecule interactions, particularly with respect to multi-site binding and binding specificity. Using different RNA aptamer constructs of a neomycin-sensing riboswitch and the aminoglycoside neomycin B, we have developed a native top-down MS approach for the localization of small molecule binding sites of RNA and their occupancy with ligand. The MS data revealed site-specific and stoichiometry-resolved information on neomycin B binding to the riboswitch aptamer that is not directly accessible by other methods, and underscore the role of noncanonical base pairs in RNA recognition. Specifically, we found that a 40 nt aptamer construct which represents the sequence with the highest regulatory factor for riboswitch function has three binding motifs for neomycin B, one corresponding to the bulge-loop motif previously determined by nuclear magnetic resonance (NMR) spectroscopy of a 27 nt aptamer construct, and the other two centered around noncanonical G•U and U•U base pairs in the lower and upper stem, respectively. In addition, the site-specific and stoichiometry-resolved occupancy data from native top-down MS experiments revealed that the populations of the three binding motifs with neomycin B can be fine-tuned by sequence mutations. For example, replacing the noncanonical G•U base pair in the lower stem with a canonical U-A base pair in the 1:1 complexes reduced binding to the corresponding binding motif from ~50% to ~30%, and introducing a CUG/CUG motif with central U•U base pair, for which neomycin B has high affinity, restored binding to the lower stem. Importantly, a single mutation in the upper stem of the riboswitch aptamer that abolishes riboswitch function reduces the occupancy of the corresponding binding motif from ~100% to ~60% in the 1:3 complexes, supporting our hypothesis that all three neomycin B molecules may play a role in riboswitch function.

In a study of viral RNA, stoichiometry-resolved native top-down MS of 1:1, 1:2, and 1:3 complexes of human immunodeficiency virus 1 (HIV-1) rev response element (RRE) RNA with neomycin B identified four distinct binding motifs and revealed preferential binding to the purine-rich internal loop motif, further demonstrating the applicability of our new approach to structural biology studies in drug discovery. We are currently extending native top-down MS, which does not require isotopic labeling, crystallization, enzymes, or chemical reagents, to other classes of RNA and ligands with the ultimate goal of establishing general principles of RNA recognition to guide the development of small molecule drugs that target RNA.

Stoichiometry-resolved, site-specific data from native top-down MS experiments, shown here for 1:3 complexes of human immunodeficiency virus 1 (HIV-1) rev response element (RRE) RNA with neomycin B (left), reveal binding motifs (right) along with their occupancies.



>> Research Grants

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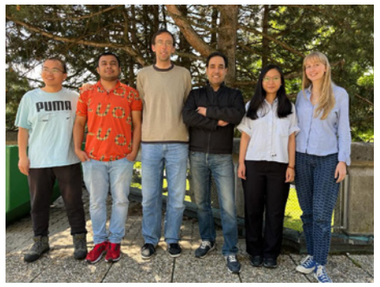
>> Coworkers

Michael Palasser, Sarah Viola Heel, Anna Ploner, Jonas Carlsson, Lena Nigsch (Ph.D. students)

Radiation damage induced by low energy electrons

Stephan Denifl

>> Department of Ion Physics and Applied Physics



>> Goal: Exploring negative and positive ion formation by secondary electrons formed upon radiation of biologically relevant compounds.

>> Background: A large number of secondary particles are generated when energetic primary radiation (e.g. photons, ions or cosmic radiation) interacts with biological material like living cells. The most abundant secondary species formed are electrons which are released with an average kinetic energy of a few eV. These electrons subsequently interact with cell components before they become a chemically inactive species. The electron interaction may however be severe even leading to damage of DNA. Therefore, it is crucial to investigate the fundamental interaction of low energy electrons with simple biomolecules representing building blocks of biological material (nucleobases, amino acids, etc.). Low-energy electrons may be also relevant for the action of radiosensitizer molecules used to sensitize hypoxic tumor cells toward highly energetic radiation. Mass spectrometry of anions formed by electron attachment represents our experimental approach.

>> Research highlights and outlook: In recent experiments we carried out mass spectrometric studies with the RRx-001 molecule (2-bromo-1-(3,3-dinitroazetidin-1-yl)ethan-1-one). This compound represents a hypoxic cell chemotherapeutic with already demonstrated synergism in combined chemo-radiation therapy. In our study we investigated, if reduction of the compound by free low-energy electrons could play an essential role. Indeed, it turned out in the course of the measurements that the molecule is highly susceptible to low-energy electrons. In addition, the single molecule in the gas phase efficiently dissociates in Br^- and NO_2^- fragment anions. Figure 1a shows the resulting Br^- anion yield as function of the initial electron energy. Dissociative electron attachment is a resonance process and thus the anion yield shows a peak-like structure. In addition, to the main peak near the electron energy of zero eV, the fitting of the data identified a second resonance in the broad tail of the zero eV peak. Quantum chemical calculations revealed the nature of these peaks and gave insight into the early dynamics in the negatively charged RRx molecule on picosecond timescales. The calculations proposed a conical intersection between $\pi^*(NO_2)$ and σ^*(C–Br) states in the negatively charged molecule (see Figure 1b and 1c), which would allow for state switching during the fast dissociation. Such initially populated states studied will be also present in solution and thus a first insight into the initial steps in the radiation chemistry of RRx was gained. In future studies, we will investigate other classes of radiosensitizer compounds in order to evaluate, if they show a similar behavior to RRx.

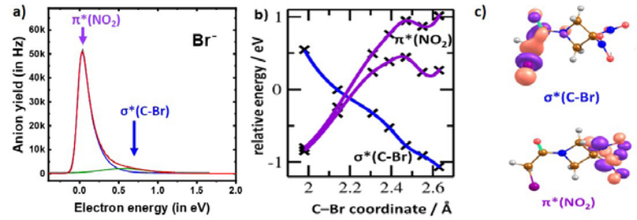


Figure 1: a) Fitted anion efficiency curve of the fragment anion Br^- formed upon electron attachment to RRx; b) Interpolation curves in the RRx anion along C–Br and C–NO_2 coordinates for the lowest three electronic states of valence character between the structure of the neutral RRx-001 molecule and pre-dissociation transition states (as optimized at the B3LYP/aug-cc-pVDZ level); c) Orbitals occupied by the odd electron for two lowest-lying valence electronic states of the RRx anion as obtained at the TD-CAM-B3LYP/aug-cc-pVTZ level. Color code: hydrogen – grey, carbon – brown, nitrogen – blue, oxygen – red, bromine – violet. Modified from Izadi *et al.*, *Angew. Chem. Int. Ed.* **63**, e202407469 (2024), CC-BY 4.0 license.

>> Research Grants

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>> Coworkers

Farhad Izadi, Muhammad Saqib, Jiakuan Chen, Debasish Parida, Vy Nguyen (Ph.D. students), Lara Schorr (student coworker)

Stem cells to unravel disease-specific mechanisms underlying neurodegenerative and neuropsychiatric disorders

Frank Edenhofer

>> Department of Molecular Biology

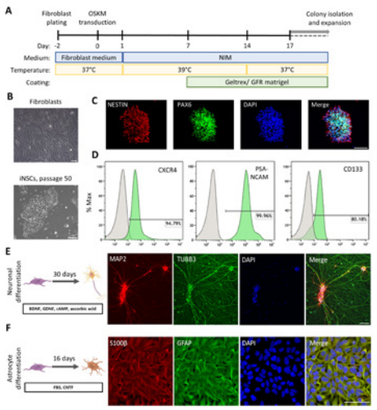

Figure 1: Induced neural stem cells (iNSCs) derived from human fibroblasts express key NSC markers and retain their neurogenic and gliogenic potential. (A) Schematic of iNSC transdifferentiation from human fibroblasts. (B) Phase contrast images of fibroblasts and derived iNSCs in culture. (C) Immunofluorescence staining of NSC markers: NESTIN, PAX6, and nuclei. (D) Flow cytometry analysis of NSC markers CXCR4, PSA-NCAM, and CD133. (E) Immunofluorescence of neurons after 30 days of differentiation, showing MAP2 and TUBB3. (F) Immunofluorescence of astrocytes after 16 days, showing S100β and GFAP. From Spathopoulou *et al., Stem Cell Rev Rep* (2024).

>> Goal: Leverage patient-derived iPSC and iNSC models to unravel disease-specific mechanisms underlying neurodegenerative and neuropsychiatric disorders.

>> Background: Neurodegenerative and neuropsychiatric disorders, including Parkinson's disease (PD), multiple sclerosis (MS), schizophrenia (SCZ), and Alzheimer's disease (AD), arise from complex genetic, metabolic, and environmental interactions. Disruptions in neurotransmitter signaling, neuroinflammation, cellular metabolism, and aging-related mechanisms contribute to disease onset and progression. Conventional models such as animal models and immortalized cell lines often fail to capture patient-specific pathophysiology. The advent of induced pluripotent stem cells (iPSCs) and induced neural stem cells (iNSCs) has revolutionized disease modeling, allowing for patient-derived, physiologically relevant in vitro systems. These models enable precise investigations into neuronal dysfunction, glial interactions, and molecular dysregulation, facilitating the discovery of novel biomarkers and therapeutic strategies tailored to individual diseases.

>> Research highlights and outlook: Our recent work advances the understanding of neurodegenerative and neuropsychiatric disorders by leveraging induced pluripotent stem cells (iPSCs) and induced neural stem cells (iNSCs) as disease models. We have successfully developed midbrain-striatum assembloids with inducible aging, providing a novel platform to study early Parkinson's disease (PD) phenotypes and the impact of aging on nigrostriatal connectivity. This model allows for the investigation of neurodegenerative progression, offering insights into age-related molecular drivers of PD pathology.

Additionally, our study on Multiple Sclerosis (MS) patient-derived iNSCs reveals that a hypermetabolic cholesterol-driven phenotype contributes to neurotoxicity via senescence-associated secretory pathways. Pharmacological intervention with statins demonstrates potential for reducing neurotoxic effects, indicating a promising translational avenue for MS therapy. Complementary to these findings, our integrative multi-omics study in schizophrenia (SCZ) identified perturbations in polyamine and GABA biosynthetic pathways, highlighting disruptions in cortical excitatory/inhibitory balance as a key pathophysiological hallmark. Finally, our exploration of miR-21-5p in Alzheimer's Disease (AD) positions this microRNA as a novel biomarker and a target for therapeutic intervention.

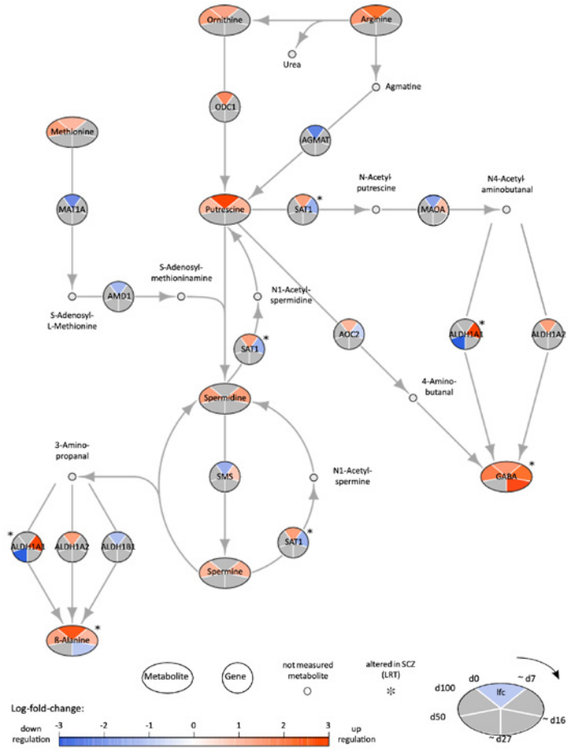

Figure 2: Transcriptomic-metabolomic integrative network reconstruction across neuronal differentiation reveals an interesting subnetwork of polyamine metabolism. Transcriptomic and metabolomic data were collected from six time points during differentiation of SCZ-derived neuronal cells, with five sequential comparisons performed to calculate statistical significance and fold change. Pathway-associated genes and metabolites were identified, integrating reaction data for network reconstruction. The final network was enriched with protein-protein interactions from the Signor database, and relevant subnetworks were extracted for further analysis. This analysis revealed a SCZ-dependent polyamine metabolism subnetwork: Metabolite abundance and gene expression changes are visualized across time points, with differentially expressed genes (circles) and metabolites (ellipses) color-coded based on log2 fold change, highlighting SCZ-specific alterations (*). From Spathopoulou *et al., Mol. Psy* (2024).

>> Research Grants

EU H2020 Marie Skłodowska-Curie COFUND doctoral training programme ARDRE, FWF Special Research Program F7804-B. FWF grant-doi: 10.55776/I5184; 10.55776/M3062, 10.55776/I4791, 10.55776/TAI801, 10.55776/T974. WINGS FOR LIFE Spinal Cord Research Foundation (WFL-AT-02/21 Proj. 242).

>> Coworkers

Christopher Esk, Francesca Finotello (Assist.-Prof.), Lisa Fellner, Katharina Günther, Marcel Tisch (postdoc); Julianne Beirute, Elisa Gabassi, Maximilian Mohr, Amelie Schurer, Gabriele Sauerwein, Angeliki Spathopoulou (Ph.D. students); Sara Campagnol, Louisa Dury, Alexander Eschlböck, Laura de Gaetano, Sabrina Höpperger, Philipp Kolb, Miriam Lechner, Theresa Lindlbauer, Kristina Plechinger, Martina Podlesnic, Antonella Rokita, Niklas Schweiger, Sandra Senn (master students); Marta Suarez Cubero, Johanna Vanacker (technicians)

Further, single-cell profiling of reprogrammed human iNSCs underscores their physiological resemblance to early neurodevelopmental progenitors, reinforcing their translational potential for modeling CNS disorders. Expanding our scope, we have established patient-specific iPSC line for vascular Ehlers-Danlos Syndrome (vEDS) and autism spectrum disorders (ASD), providing a foundation for future research on connective tissue pathophysiology and neurodevelopmental disease.

Moving forward, we aim to integrate patient-derived organoid models with high-resolution single-cell and multi-omics analyses to refine our understanding of aging in the CNS in general, as well as neurodegeneration and psychiatric disorders. This approach will enable us to identify novel disease mechanisms and therapeutic targets, ultimately driving innovation in regenerative medicine and personalized treatment strategies.

Stem cells, regeneration, and bioadhesion in basal animal model systems

Bert Hobmayer and Peter Ladurner

>> Department of Zoology

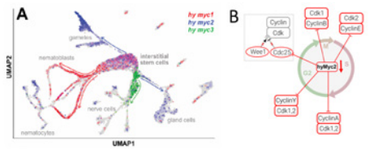

Figure 1: Myc2 as a c-Myc like master control factor for cell proliferation in adult stem cells in ancestral *Hydra* polyps. (A) Expression patterns of the three *myc* genes in self renewing interstitial stem cells and gamete precursors (*myc2*), in differentiating stinging cells/nematoblasts (*myc1*), and in neurosecretory precursors (*myc3*) according to the *Hydra* single cell transcriptome atlas. (B) Knockdown of *myc2* using RNA interference inhibits cell proliferation and down-regulates most cell cycle-promoting genes.

From Cazet et al. *Genome Research* 33: 283-298 (2023).

>> Goals: (1) We want to characterize decision-making in stem cell lineages and the roles stem cells play during animal development and during regeneration and tissue replacement. (2) We want to characterize the structure of naturally occurring glue proteins in order to establish synthetic counterparts.

>> Background: We work with simple model organisms such as cnidarian polyps, flatworms, and sea squirts. We study cellular and molecular aspects of positional signaling, regeneration of lost body parts, and bio-adhesion. We analyze conserved signaling pathways and transcription factors to gain a better understanding of principle molecular mechanisms. We project our findings on an evolutionary scale across animal phyla. This transfer of knowledge from ancestral models to higher organisms may point to potential targets for biomedical research.

>> Research highlights and outlook: The cnidarian polyp *Hydra* is a classic model for stem cell and regeneration research. One of the three types of adult stem cells, the interstitial stem cell, shows multi-potency giving rise to somatic differentiation products such as nerve and stinging cells, as well as the gametes. Notably, interstitial stem cells proliferate and self-renew constantly and indefinitely without showing any sign of cellular senescence. Using gene-specific knockdown and BrdU continuous labelling assays, we have now identified the constantly activated *Hydra* Myc2 protein as a c-Myc-type master regulator of cell cycle progression in our stem cells. We aim at characterizing the molecular networks regulated by Myc2. RNA-seq data suggest that not only cell cycle control genes including Cyclins and Cdks are under control of Myc2, but also gene networks acting in ribosome biogenesis and stem cell pluripotency. We now intent to expand our analysis to various omics screenings at a single cell level.

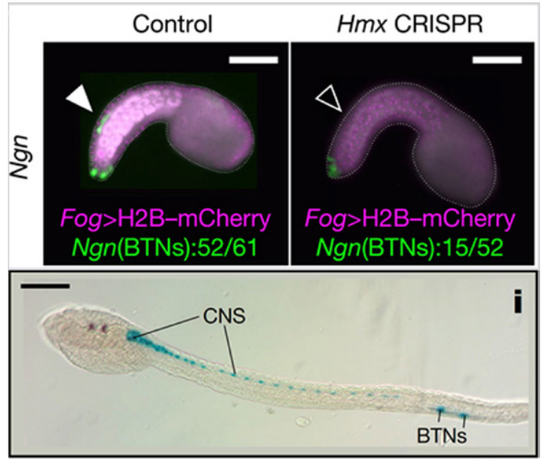

Figure 2: Hmx functional and regulatory conservation between the proto-vertebrate *Ciona* (urochordates) and the vertebrate stem lineage (lamprey). Upper panel: the Hmx transcription factor is essential for *Ciona* sensory bipolar tail neurons (BTNs) upstream of neurogenin (Ngn) and driving the head placodal sensory programme in vertebrates (not shown). Lower panel: a lamprey Hmx enhancer drives similar territories in ascidians showing that deep conservation of upstream regulatory networks spans the evolutionary origin of vertebrates.

From Papadogiannis, V. et al. *Nature* 605 (2022): 701-705.

We have characterized the two major adhesive glyco-proteins of the flatworm *Macrostomum lignano* using a transcriptomic and high throughput *in situ* screening approach combined with mass spectrometry, confocal and electron microscopy, RNA interference, specific antibodies and lectin staining. We are currently using single-cell RNA-seq to obtain a genetic fingerprint of the releasing gland cell. Our aim is to characterise the molecules involved in the flatworm release mechanism. The aim is to understand the mode of action of these molecules to enable the development of new synthetic counterparts - reversible adhesives for biomedical applications.

To complement our research with expertise for genetic regulation and promoter analysis, Ute Rothbächer works with sea squirts, a vertebrate sister group and model organism for functional genomics. She studies the controlled exit of embryonic stem cells from pluripotency towards nervous or epidermal cell fate and takes advantage of efficient gene transfer techniques (electroporation, microinjection), *in silico* data bases, and sophisticated functional genomics tools. Using gain- and loss-of-function (CRISPR/Cas9), we have defined novel transcriptional repressor mechanisms influencing neuro-ectodermal enhancers and also demonstrated an evolutionary conserved role of the Hmx gene in sensory neuron formation. Within the head neural placode we study the larval sensory adhesive organ and its underwater glues capable of attachment in wet and salty conditions. Such materials may inspire medical adhesives or anti-fouling substances in the future.

>> Research Grants

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>> Coworkers

Ute Rothbächer (Assoc. Prof.); Bernhard Egger (Assis. Prof.); Anna Seybold (Senior Scientist); Birgit Lengerer, Attila Szucs, Fan Zeng (PostDoc); Philip Bertemes, Alexandra Grosbusch, Isabel Dittmann, Moses Kitilit Kibet, Alessandro Pennati, Marion Lechable, Matthias Achrainer (PhD students); Magdalena Knapp (electron microscopy); Natalie Kolb, Bianca Horrer, Dzenana Tufegzic, Angelika Hildebrand (technician and animal culture)

Stress response to environmental stress in earthworms

Martina Höckner

>> Department of Zoology

>> Goal: To understand the molecular stress response to changing environmental conditions with a special focus on regulation and immunity in soil dwelling organisms like earthworms.

>> Background: Understanding how organisms respond and adapt to environmental changes is crucial in times of rapidly changing global conditions. The mechanisms and regulatory networks responsible for coordinated stress responses in a wide range of invertebrate species have been largely neglected. This gap has resulted in a limited knowledge of the evolutionary and functional aspects of cellular processes involved in coping and adaptation strategies, particularly in response to toxic metals like cadmium (Cd) and physical stressors such as injuries. Stress-induced effects are often linked to epigenetic factors and metabolism, however, little is known about these processes in invertebrates like earthworms.

>> Research highlights and outlook: Our studies revealed that even low levels of Cd exposure cause DNA hypermethylation in earthworms, although common mechanisms for maintaining or de novo DNA methylation remain unaffected. Notably, coelomocytes—earthworm immune cells—play a central role in both detoxification and wound healing processes. Injury can modulate detoxification pathways, indicating a dynamic interplay between immune response and stress adaptation mechanisms. These findings offer new insights into the coordination of molecular stress responses, with broader implications for stress resilience in environmental toxicology and regeneration biology.
Moving forward, we will focus on the cell type composition and functional diversity of earthworm coelomocytes using single-cell RNA-seq and ATAC-seq analyses. Preliminary studies have shown that non-invasive harvesting of immune cells and the immediate availability of single-cell suspensions make earthworms an ideal experimental model to apply single-cell technologies. Initial data have revealed several distinct cell clusters (Figure 1), suggesting that coelomocytes participate in a wide range of biological processes.

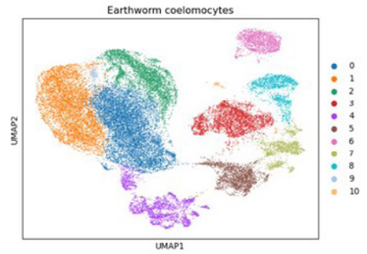


Figure 1: Clustering analysis of single-cell RNAseq data from *L. terrestris* coelomocytes and visualization using UMAP, a commonly used dimensional reduction technique. Eleven coelomocyte cell clusters have been identified (unpublished data).

>> Research Grants

FWF Einzelprojekt P33835-B Role of earthworm MTs in stress response and innate immunity; L'Oreal PostDoc grant, Veronika Pedrini-Martha; Lise Meitner Projekt I 3136-B29, Maja Šrut

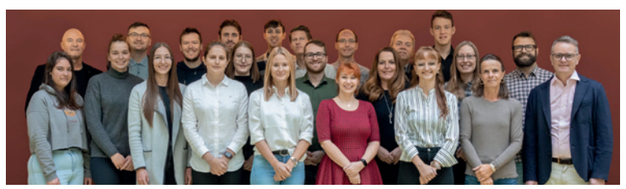
>> Coworkers

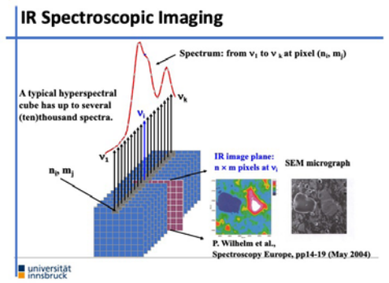
Maja Šrut, PostDoc; Veronika Pedrini-Martha, PostDoc; Claudio Piechnik, PostDoc; Gerhard Aigner, PhD student; Luis Põtzl, master student; Veronika Peer, Wissenschaftliche Mitarbeiterin; Birgit Fiechtner, technician

Advanced analytical tools for natural product and bioanalysis

Christian W. Huck

>> Department of Analytical Chemistry and Radiochemistry

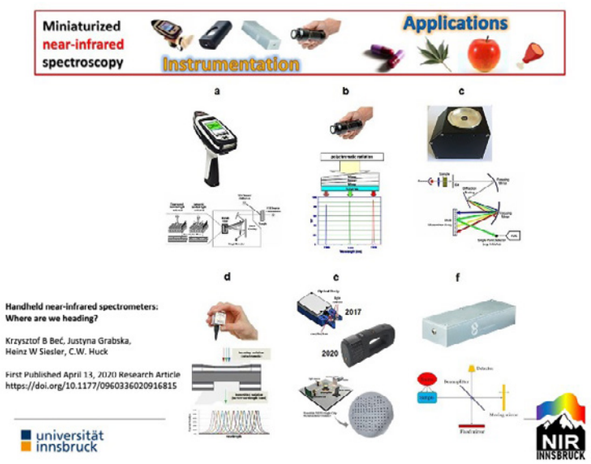




>> Goal: Christian W. Huck's research focuses on advancing vibrational spectroscopy techniques, particularly near-infrared (NIR), mid-infrared (MIR), and Raman spectroscopy, for applications in biomedical diagnostics, food authentication, pharmaceutical analysis, and environmental monitoring.

>> Background: The group integrates near-infrared (NIR), mid-infrared (MIR), and Raman spectroscopy with chemometric data analysis to enhance applications in biomedical diagnostics, pharmaceutical quality control, food authentication, and environmental monitoring. Their interdisciplinary approach combines analytical chemistry, spectroscopy, and artificial intelligence to develop innovative, non-invasive, and real-time detection methods. The team collaborates extensively with international research institutions, industry partners, and medical professionals to translate laboratory findings into practical applications. Key research areas include pathogen detection, microplastic analysis, hyperspectral imaging, and portable spectroscopy for rapid diagnostics. With a strong focus on applied analytical chemistry, the group contributes to advancing spectroscopy-based solutions for global health, safety, and sustainability challenges. Under Professor Huck's leadership, the team remains at the forefront of cutting-edge spectroscopic research, fostering innovation in multiple scientific domains.

>> Research highlights and outlook: Key highlights from their recent work include the development of **non-invasive diagnostic tools** for biomedical applications, such as using Raman spectroscopy for rapid pathogen detection in infections and hyperspectral imaging for forensic investigations. In **food science**, the group has advanced spectroscopic techniques for quality assessment and authentication, notably in the verification of Iberian ham breeds and the detection of adulterants in food products. Their research in **pharmaceutical analysis** has enabled efficient screening of active compounds in herbal medicines and dietary supplements. Furthermore, **environmental monitoring** remains a focus, with studies on microplastic detection in various ecosystems using advanced spectroscopic approaches. Looking forward, the research group aims to enhance the integration of spectroscopy with **artificial intelligence (AI) and machine learning**, improving automation, accuracy, and predictive capabilities. Expanding the use of **portable and handheld spectroscopic devices** for real-time field applications will further drive impact in clinical diagnostics, food safety, and environmental monitoring. By fostering interdisciplinary collaborations and technological advancements, the group continues to push the boundaries of analytical chemistry, paving the way for innovative, real-world applications.



>> Research Grants

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>> Coworkers

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Cellular Senescence in Ageing and Disease

Pidder Jansen-Dürr

>> Research Department for Biomedical Aging Research

>> Goal: To obtain an integrated understanding of molecular and cellular mechanisms underlying cellular senescence and ageing in mammals.

>> Background: The ageing process is modulated by a complex network of interacting genetic pathways, which have been elucidated through studies on lower eukaryotic model organisms. In vertebrates, the concept of cellular senescence has gained a lot of impact in the last decade primarily by the discoveries that i) cellular senescence occurs in aged organisms from primitive vertebrates up to humans, and ii) the recent demonstration that the accumulation of senescent cells in mouse models drives the ageing process. Recent progress in biogerontology suggests that mitochondria, cellular organelles best known for their ability to generate energy in form of ATP from dietary nutrients, take center stage in many processes driving ageing.

>> Research highlights and outlook:

A. Cellular senescence in skin aging

Previous work established that the cellular senescence induced by UVB irradiation in human dermal fibroblasts induces autophagy; blocking of autophagy shifted the fate of UVB-treated cells from senescence to apoptotic cell death. In the reporting period the group has identified a key role of mitochondrial quality control in stress-induced premature senescence of HDF and identified the mitophagy receptor NIX as a key player in controlling mitochondrial function to allow survival and senescence of UVB treated dermal fibroblasts. Genetic inactivation of NIX was sufficient to induce premature senescence in untreated cells and switched cell fate of UVB treated cells from senescence to apoptotic cell death, both in a 2D model of UV-induced Photoaging and in reconstructed human skin. Additionally, we identified a key role for mitophagy and the secretion of extracellular vesicles as quality control mechanisms shifting the fate of stressed cells from cell death to senescence[1]. These results suggest a key role of mitochondrial quality for survival of senescent cells, with potential implications for the development of new strategies to prevent UV-induced photoaging of the skin.

We also demonstrated that the combined exposure of human dermal fibroblasts to UV radiation and urban particulate matter (UPM) leads to mitochondrial dysfunction, increased ROS production, and DNA damage. While UPM alone had minimal effects, its co-exposure with UV selectively inhibited autophagic flux, shifting cellular fate from senescence to apoptotic cell death. These findings underscore the synergistic impact of UV and pollution on skin aging and highlight

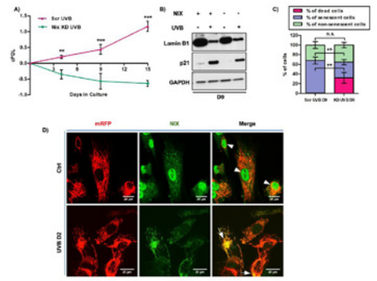

Fig 1. NIX KD leads to sustained mitochondrial damage and changes the fate of UVB-irradiated fibroblasts from senescence to cell death.
Fibroblasts were transduced with lentiviral vectors carrying NIX or scrambled shRNAs and grown under selection. Resulting NIX KD and Scr cells were irradiated twice a day for 4 days and monitored for cell growth (a), expression of senescence-related proteins (b) and activity of SA-β-Gal (c). (a) Cumulative population doublings of the given populations represent mean values of three independent experiments ± SD. (b) WB to evaluate the expression of Lamin B1 and p21 in UVB-irradiated Scr and NIX-depleted HDF. GAPDH was used as loading control. (c) SA-β- gal cytochemistry for detection of senescent cells. Number of dead cells was counted by Casy counter. (h) Fibroblasts expressing mRFP (red) irradiated for 2 days (UVB D2) and the corresponding control (Ctrl D2) were fixed and processed for indirect immunofluorescence. NIX was detected with appropriate antibodies and is shown in green. Overlaying of the two channels was obtained by the microscope software and co-localization is characterized by yellow color (white arrows).

the importance of autophagy in cellular stress responses[2]. We also identified CLCA2 as a novel regulator of cellular senescence and skin homeostasis. CLCA2 expression was upregulated in UVB- and Nutlin3a-induced senescence, while its depletion accelerated senescence onset, altered the secretome profile, and induced aged-like features in 3D skin equivalents. These results suggest a protective role for CLCA2 in preventing premature skin aging[3]. Finally, we investigated the function of GDF15 in mitochondrial homeostasis and senescence. Loss of GDF15 in human dermal fibroblasts induced mitochondrial dysfunction and premature senescence, accompanied by a distinct secretory phenotype. In 3D human skin models, fibroblast-specific GDF15 depletion led to epidermal thinning, a hallmark of skin aging[6]. These findings highlight GDF15 as a critical factor in maintaining mitochondrial function and delaying age-associated skin changes.

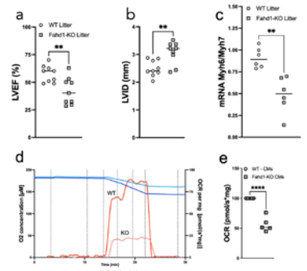

Fig. 2: Loss of FAHD1 influences heart function and development. (A) Results of echocardiography in WT and Fahd1-KO mice. Fahd1-KO mice display increased left ventricle internal dimension (LVID) and decreased left ventricle ejection fraction (LVEF), n=9. (B) Isolated cardiomyocytes from Fahd1-KO mice have decreased complex II activity compared to WT counterparts. Oxygen consumption rates of WT and Fahd1-KO cardiomyocytes were measured by high resolution respirometry. The timeline shows the addition of different substrates for determination of complex II activity (right panel). ROT (rotenone), ADP, SUC (succinate), DIG (digitonin), MNA (malonic acid), AmA (antimycin A). Quantification of complex II activity and expression as percentages (left panel), n=3. (C) Ratio of expression of Myh6 to Myh7 mRNA in WT and Fahd1-KO hearts, n=6.

>> Research Grants

FWF 10.55776/FG24; EU Horizon 2020 MSCA-CO-FUND 847681; TWF F.50279; TWF F.49076; NIH URM #P30AR069625; LFUI ESF W-174607; TNF F.47939/5-2023; LFUI NF-74600-013;TWF 2021-F.33827/10-2021;LFUI Swarovski 281886; BBSRC BB/X017966/1; LFUI 2021-/1/BIO-1; LFUI 2020/2/BIO-5; LFUI 2019/1/BIO-6

>> Coworkers

Maria Cavinato (Co-PI); Athanasios Seretis (postdoc); Sophia Wedel, Max Holzknecht, Ines Martic, Elia Capuccio, Nikolaus Pittl (Ph.D. students); Teresa Zenleser, Juliane Gasser, David Feldman, Amina Hassan, Dona Simeoni (MSc students); Tabea Grimm, Felix Merler, Evelyn Mazzarano (diploma students), Ayse Öztürk (technician)

B. FAHD1 – a new regulator of mitochondrial function

The FAH superfamily of metabolic enzymes contains many prokaryotic enzymes catalyzing a broad variety of related but distinct chemical reactions, including a bona fide oxaloacetate decarboxylase (ODx) identified in *Corynebacterium glutamicum*. Of note, besides the name-giving enzyme fumarylacetoacetate hydrolase (FAH), two additional members of the FAH superfamily were identified in eukaryotes, including FAH domain containing protein 1 (FAHD1). We found that FAHD1 is localized in mitochondria and displays oxaloacetate tautomerase/decarboxylase activity, rendering this enzyme a potential new regulator of metabolic flux through the TCA cycle, acting as an antagonist of the anaplerotic enzyme pyruvate carboxylase (PC)[x]. Of note, we found that knocking down FAHD1 expression in human endothelial cells induced premature senescence in these cells, suggesting that FAHD1 is a novel regulator of mitochondrial function and cellular senescence.

In the reporting period, the group has established a critical role for FAHD1 to promote survival of triple negative breast cancer cells[7]. In an ongoing project, the role of FAHD1 has been investigated in regard to cardiomyocyte function. Preliminary results from our group have demonstrated that Fahd1-KO hearts have increased left ventricle size while displaying reduced left ventricle ejection fraction (Fig 2A). Further investigation has shown that Fahd1-KO cardiomyocytes have reduced activity of complex II and show signs of delayed maturation, such as reduced expression of the adult myosin isoform, myosin heavy chain 7 (Myh7) and increased expression of the embryonic isoform, myosin heavy chain 6 (Myh6) compared to their WT counterparts (Fig 2B and C) (unpublished data).

Finally, the role of FAHD1 is being investigated in the context of humoral immunity. Preliminary data from our group demonstrate that FAHD1 is expressed by B lymphocytes. Whereas flow cytometry analysis of resting mouse spleens revealed no difference in the proportions of B cells between WT and Fahd1-KO mice, we identified a reduction of proliferating, activated germinal center B cells in Fahd1-KO mice compared to WT. These data suggest that the loss of FAHD1 activity could have an impact on the development of high-affinity antibodies against pathogens and humoral immunity in general (unpublished data).

Computational investigation of protein mutations

Teresa Kaserer

>> Department of Pharmacy, Pharmaceutical Chemistry Section

>> Goal: The development and application of computational tools for the investigation of protein mutations.

>> Background: Many aspects of protein function can be altered by mutations and computational investigation and prediction of these effects can be used in multiple ways. Our lab focuses on two aspects: the identification of cancer drug resistance mutations and the development of novel gene therapies.

While the discovery of targeted cancer drugs was a break-through in cancer therapy, resistance almost inevitably occurs. Among the many molecular mechanisms conferring drug resistance is also mutation of the drug target and our group therefore develops and applies novel computational methods to identify clinically relevant resistance mutations before they emerge in patients. This allows, among other things, the timely discovery of novel and effective treatment alternatives in a timely manner. In addition, we use our developed methods to deliberately introduce mutations into proteins to alter their function in a way that makes these proteins suitable for gene therapy applications.

>> Research highlights and outlook: One aim of our lab is the continuous improvement of existing, as well as the development of novel workflows. This includes also our previously reported method to prospectively predict drug resistance mutations within the ligand binding site, where we have for example improved the final prioritization of likely patient mutations by introducing a Pareto ranking procedure. In addition, we have developed a novel workflow, which we called "Disruptor" to identify oncogenic patient mutations, which confer their disease-causing effects via the disruption of protein-protein or protein-nucleic acid interactions.

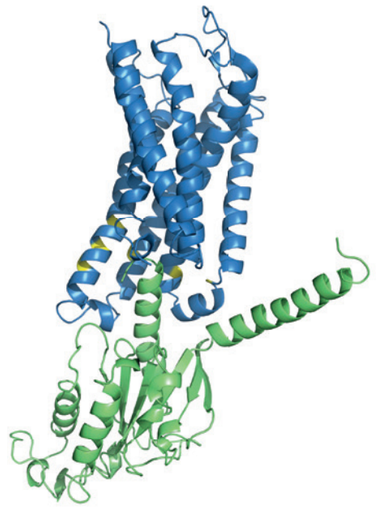

Figure 1. Structural model of the KOR (blue) in complex with the $G\alpha_{i1}$ subunit (green). The residues that were mutated are highlighted in yellow. Please note, that some of them are located outside of the receptor-$G\alpha_{i1}$ binding interface and thus affect G-protein binding via an allosteric mode of action.

>> Research Grants

FWF FG24, FWF P34376, FWF P35579, FWF P35722, TWF F.18676

>> Coworkers

Siriwat Hongnak, Michael Langeslag (postdoc); Julia Baumann, Helge Schöppe (Ph.D. students); Sarah Brouceck, David Ebert, Lukas Forster, Madeline Hofer, Anna Huber, Carina Kaltenböck, Alina Lersch, Jasmin Neumann, Jasmin Neunhäuserer, Larissa Troger, Isabella Weisleitner, Julia Wolf (master students), Elena Gil Gutierrez, Nicole Croci (international students)

In collaboration with Emmanuel Heilmann from the Medical University Innsbruck (MUI), we explored the applicability of our drug resistance prediction methods outside of cancer. In three publications, we have investigated the molecular mode of action of experimentally identified mutations in the Sars-CoV-2 and MERS main proteases, which confers resistance to available main protease inhibitors.

Together with the lab of Andreas Lieb at the MUI we are working on the development of novel designer receptors suitable for gene therapy. We focus here on protein-ligand target complexes tailored for a specific disease and aim to improve the opportunities for clinical translation of the novel technologies. Along those lines, we also investigate the basic biology of the proteins of interest, to better understand their function and hence how it can be modulated. For example, we used the kappa opioid receptor (KOR) as a model protein for G protein-coupled receptors to study the molecular determinants of preferential G protein coupling. Here we observed that all of our introduced mutations altered G protein preferences, however, each single mutant or mutant combination showed a unique effect.

The development of novel computational methods to expand the repertoire of drug resistance mechanisms we can analyze is one of the most important research goals for the near future. For example, we are currently finalizing a procedure to predict both oncogenic and drug resistance mutations which mediate their effect via an allosteric molecular mechanism. In addition, the rational and disease-specific engineering of novel designer receptors for gene therapy together with the Lieb Lab remains one of the central aims of our research efforts.

Translating lipidomics into therapeutic frontiers

Andreas Koeberle

>> Former Michael Popp Institute

>> Goal: Uncovering the interconnection of lipid metabolism, signal transduction, and homeostasis to advance the development of biogenic drugs.

>> Background: Our research lies at the convergence of inflammation, cancer, lipid metabolism and lipid signaling, with a focus on elucidating the molecular mechanisms of natural products, particularly biogenic small molecules. Through the application of cutting-edge (bio)analytical, biochemical and molecular pharmacological techniques, we are dedicated to uncovering novel drug targets and advancing biogenic lead structures. In addition, our exploration of natural products extends to investigating the physiological role of their targets in cellular processes associated with chronic inflammation and programmed cell death. Central to our interdisciplinary approach is the use of advanced chromatographic and mass spectrometric bioanalytics of lipids, specifically targeted lipidomics. This powerful method allows us to delve into the intricate interplay between lipid metabolism, signal transduction and homeostasis, shedding light on previously uncharted territory.

>> Research highlights and outlook: Research at the MPI involves pioneering therapeutic strategies focused on combatting therapy-resistant cancer by addressing stress-adaptive mechanisms and intervening in cell death-associated degeneration and necroinflammation. Through collaboration with partners from Erlangen, our investigations revealed that mesenchymal-like cancer cells, which exhibit heightened metastatic capacity, aggressiveness, and therapy resistance, become particularly susceptible to ferroptotic cell death due to reprogramming of fatty acid metabolism and membrane composition triggered by epithelial-mesenchymal transition (EMT) (Figure 1). Our quest for biogenic small molecules capable of modulating membrane lipid composition led to the discovery of a general mechanism through which cytotoxic stress sensitizes membranes to oxidative damage and the identification of stress-protective signaling lipids derived from phospholipids. These findings present promising avenues for more effective therapeutic strategies targeting fatty acid/phospholipid metabolism alongside ferroptosis induction.

Furthermore, our drug discovery program has successfully unveiled innovative ferroptosis-inducing and -inhibiting agents that leverage redox cycles to generate oxygen radicals for ferroptosis propagation or regenerate lipophilic radical traps to inhibit ferroptosis at catalytic concentrations. Additionally, we have identified natural products capable of inducing a switch in lipid mediators, along with other metabolic adaptations, with the potential to inhibit inflammation while actively promoting inflammation resolution, thereby aiming for enhanced tissue regeneration in degenerative liver disease.

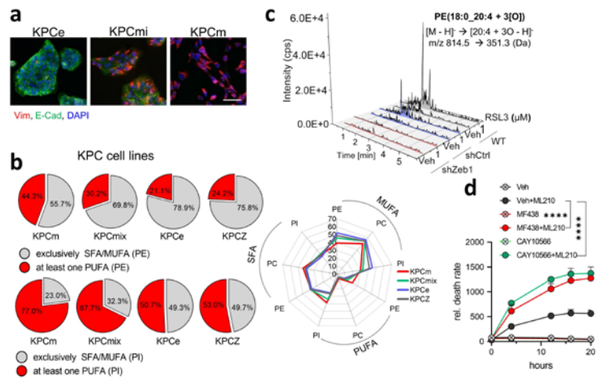

Figure 1: Targeting fatty acid metabolism to exploit the vulnerability of EMT-driven therapy-resistant cancer to ferroptosis. (**a**) Tumor-derived epithelial (e), mesenchymal (m), and mixed-type (mi) pancreatic cancer cells stained with markers. (**b**) Higher proportion of polyunsaturated fatty acids (PUFAs) in mesenchymal cells. (**c**) Mesenchymal cells are more sensitive to peroxidative membrane damage. (**d**) Targeting fatty acid biosynthesis and shifting the membrane PUFA ratio sensitizes cancer cells to ferroptosis inducers.

>> Research Grants

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>> Coworkers

Ehsan Bonyadirad, Solveigh Koeberle, Zhigang Rao, Fengting Su, Lorenz Waltl (senior scientists/ postdocs); Leonhard Bereuter, Minh Bui-Hoang, André Gollowitzer, Stephan Permann, Fengting Su, Lorenz Waltl, Finja Witt, Loc Le Xuan (PhD students); Felix Benscheidt, Julia Grander (technical assistants)

Pharmacotherapeutic potential of retinal L-type calcium channels

Alexandra Koschak

>> **Department of Pharmacy, Pharmacology and Toxicology Section**

>> Goal: Explore the pharmaco-therapeutic potential of voltage-gated Cav1.4 L-type calcium channels for gene therapeutic treatment of retinal diseases.

>> Background: Cav1.4 L-type calcium channels (LTCCs) serve as the predominant source for Ca^{2+} entry in photoreceptors and retinal bipolar cell because they allow sustained release of glutamate at their synaptic sites which are specialized ribbon synapses. They activate rapidly at moderately negative voltages and exhibit slow inactivation to enable such a tonic release. Of note, accessory Cavβ subunits are essential for surface expression of Cav1.4 LTCC complexes and crucially modulate biophysical properties like voltage-dependent inactivation. Studies highlighted the importance of Cav1.4 for the assembly and maintenance of the retinal ribbon synapse. Importantly, pathogenic variants of the encoding *CACNA1F* gene have been associated with a number of retinal diseases, among those is congenital stationary night blindness type 2 (CSNB2).

>> Research highlights and outlook: Our recent study has examined two pathogenic *CACNA1F* variants that neutralize gating charges in the S4 voltage sensor (exchanging arginine 964 with glycine or arginine 1288 with leucine (RL in the following; Heigl et al. (2023)). In both, charge neutralization was associated with a reduction channel expression also reflected in smaller ON gating currents. In RL channels the strong decrease in whole-cell current densities might additionally be explained by a reduction of single channel currents. We further identified alterations in their biophysical properties, such as a hyperpolarizing shift of the activation threshold and an increase in slope factor of activation and inactivation. Molecular dynamic simulations in RL substituted channels indicated water wires in both, resting and active, channel states suggesting the development of omega currents as a new pathological mechanism in CSNB2. This sum of the respective channel property alterations might add to the differential symptoms in patients beside other factors such as genomic and environmental deviations.

To gain a deeper understanding of the impact of various *CACNA1F* mutations, we are currently investigating how different Cav1.4 variants affect retinal function and structure along with proteome composition. By integrating in vivo models with advanced techniques such as label-free quantitative proteomics, we aim to understand whether the varied impacts observed across different Cav1.4 variants are reflected in the protein composition of the retina, potentially providing insights into the variable clinical manifestations of CSNB2. Our findings suggest that the variation in dysregulated proteins may play a significant role in determining differences in disease severity, offering a potential mechanism for predicting the intensity of the disease in individual cases. Still, the development of gene therapy for *CACNA1F*-related disorders encounters a significant challenge due to the size of the *CACNA1F* gene, which exceeds the packaging capacity of a single AAV vector. To address this limitation, we must explore alternative strategies, such as utilizing dual AAV vector systems or investigating other gene delivery methods capable of handling larger genetic material. Non-viral gene therapy may also offer a safe and effective option. Together with our local collaborators we developed phosphatase-responsive zeta potential converting nanocarriers utilizing polyphosphate-coated cell penetrating peptide-decorated nanoemulsions as a promising gene delivery system to retinal cells (Nguyen et. al., 2022). Further advancements will be crucial in translating basic research findings into effective therapies for retinal channelopathies associated with Cav1.4 dysfunction.

We also described the discovery and characterization of a novel *CACNAB2* variant which encodes for Cavβ2 accessory subunits with distinct features (Seitter et al., 2023). We called the novel splice variant Cavβ2i and showed that it predominates in the retina with expression in photoreceptors and bipolar cells. Of note, the Cavβ2i N-terminus exhibits an extraordinary concentration of hydrophobic residues, a feature not seen in canonical variants. The biophysical properties resembled known membrane-associated variants, however, Cavβ2i exhibited both a strong membrane association and a propensity for clustering which depended on hydrophobic residues in its N-terminus. We considered available Cavβ structure data to elucidate potential mechanisms underlying the observed characteristics but resolved N-terminus structures were lacking and thus, precluded clear conclusions. With our report, we expand the scope of functional variation through N-terminal splicing with a distinct form of membrane attachment. Further investigation of the molecular mechanisms underlying the features of Cavβ2i could provide new angles on the way Cavβ subunits modulate LTCCs at the plasma membrane.

>> Research Grants

To Alexandra Koschak: FWF 36262, FWF 32747, DOC30 Doc funds (PhD program CavX). To Matthias Ganglberger: ÖAW P26621

>> Coworkers

Matthias Ganglberger, Elisa Roth, Abdallah Abdalhady, Kathrin Spielvogl (PhD students); Patrick Malcher, Christoph Ittlinger (Master students; 01-2025 only); Mareike Uthoff (technician) and Bettina Tschugg (technician, currently in parental leave)

Plant biochemistry and metabolism

Ilse Kranner

>> Department of Botany

>> Goal: To deepen our understanding of the regulation of plant metabolism with the aim to identify key molecular switchboards that determine plant stress response.

>> Background: Photosynthetic organisms underpin nearly every form of life on our planet: every organic carbon compound originates from CO_2 assimilated through photosynthesis, and this process has also generated the atmospheric O_2 on Earth, essential for aerobic respiration. Despite significant gains in global crop yields over recent decades, climate change, associated with rising temperatures and increasingly more erratic rainfall, has begun to stall this progress and casts a troubling outlook on future productivity of global ecosystems.

Our laboratory seeks to dissect the molecular networks that enable plants to withstand environmental stress factors. One avenue of our research examines how climatic shifts affect seed quality and performance in higher plants, while another explores the metabolic strategies that allow alpine plants to thrive in the habitats characterized by extreme fluctuations in environmental conditions. Responses of key tree species in mountain forests are a specific focus for studying the impacts of recurrent droughts and elevated temperatures. During drought, stomatal closure driven by abscisic acid suppresses key pathogen-defence pathways, increasing tree susceptibility to biotic stress factors. As a consequence, our woodlands face heightened impacts from insects such as bark beetles and microbial pathogen such as the needle bladder rust, caused by the fungus *Chrysomyxa rhododendri*. We are also probing the bi- or multidirectional chemical signalling between plants and their associated microbiota, within lichen symbioses and seed endophyte communities.

Methodologically, we combine broad-spectrum approaches, such as GC-MS-based untargeted metabolite profiling, with targeted assays for antioxidants, photosynthetic pigments, flavonoids, fatty lipids and phytohormones using UHPLC-MS/MS and HPLC. Complementary spectrophotometric analyses help us pinpoint key metabolic checkpoints that govern growth, development, and stress resilience. Our experimental systems span well-established models like *Arabidopsis thaliana*, a model higher plant, and the unicellular gree algae *Chlamydomonas reinhardtii*. These models provide rich genetic toolsets and mutant collections, alongside major crops, such as sunflower, cabbage, wheat and barley, and a diverse panel of native alpine taxa, including spruce, larch, pine and juniper.

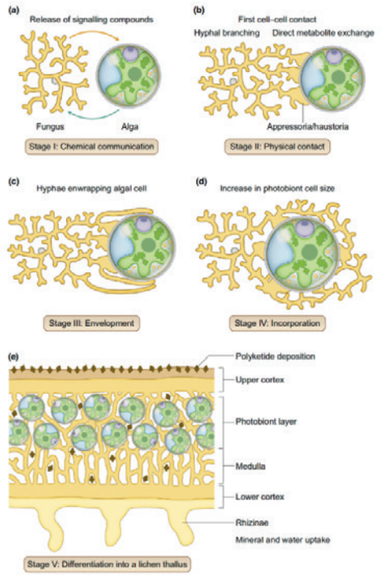

Figure 1. The stages of lichenization. (a) In the precontact stage, before physical interaction, hyphal branching is observed and both partners release signalling molecules into the environment that support mutual recognition; (b) during the contact stage, the fungus develops appressoria and haustoria between hyphae and photobiont cells, permitting direct metabolite exchange; (c) in the envelopment stage, fungal biomass expands, additional appressoria and haustoria develop, and hyphae envelop the photobiont cells; (d) during the incorporation stage, fungal hyphae and algal cells aggregate into undifferentiated clusters and algal cell volume increases; and (e) in the differentiation stage, these clusters develop into a fully formed lichen thallus. From Pichler et al. 2023. *New Phytologist* **238**: 1362-1378. https://doi.org/10.1111/nph.18780

>> Research Grants

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>> Coworkers

Thomas Roach (Associate Professor); Erwann Arc (Senior Scientist); Gregor Pichler, Clara Bertel (Postdocs); Nicki Marami-Zonouz, Hooman Norouzi, Anna Pfleger, Moritz Stegner (PhD students); Otto Dämon, Birgit Knoll, Bettina Lehr, Christine Rossetti (Technicians)

>> Research highlights and outlook: As part of the FWF project "The lichen symbiosis: Metabolites involved in lichenization", we assessed the chemical communication between fungi and algae required to form a lichen. Lichens are regarded as self-sustaining micro-ecosystems formed by the interaction of an exhabitant fungus, called 'mycobiont', forming a symbiosis with extracellular microbial photosynthetic partners, termed 'photobiont', and an indeterminate number of other microscopic organisms. Lichens produce a plethora of secondary compounds, e.g. depsides and depsidones, some of which are of potential pharmaceutical interest due to their antiviral, antibacterial and antifungal properties, and are usually exclusively produced in symbiosis. However, lichens are notoriously difficult to culture and are among the slowest growing organisms known. In addition, the molecular signals that drive the transition from free-living fungi and microalgae to a unified thallus, termed lichenization, and those that sustain the symbiosis remain poorly characterized. In the prestigious Tansley reviews series, we presented an integrative signalling model for lichenization encompassing five sequential stages (Fig. 1). Early recognition appears to be orchestrated by fungal lectins and algal cyclic peptides, whereas phytohormones, antioxidant systems and sugar/sugar-alcohol transport underpin maintenance of the symbiosis. In the fully differentiated thallus, specific secondary metabolites and mineral nutrition provided by the mycobiont are suggested to consolidate thallus integrity and nurture its microbiota. This framework is now guiding the improved culture methods for these fastidious organisms, laying the groundwork for future pharmaceutical discoveries in follow-up projects.

In another project, we used trees from very rare Norway spruce genotypes that are resistant to the needle rust fungus *Chrysomyxa rhododendri*, offering both practical propagation potential and a unique opportunity to study molecular defence mechanisms. Combining RNA-Seq, RT-qPCR and secondary metabolite profiling to dissect constitutive and induced responses, we found that the resistant genotype diverged from susceptible trees in both gene expression and metabolite patterns. Several defence-related genes, encoding endochitinases, chitinases and other antifungal proteins, were upregulated constitutively and upon infection in the resistant genotype, which also accumulated higher levels of flavonoids, such as kaempferol and taxifolin, as well as stilbenes, geranyl acetone, α-ionone, abscisic acid and salicylic acid. The resistant genotype's combination of strong baseline defences and robust induced responses highlights key genetic and metabolic traits for breeding rust-tolerant spruce.

Biomolecular NMR of nucleic acids

Christoph Kreutz

>> Department of Organic Chemistry

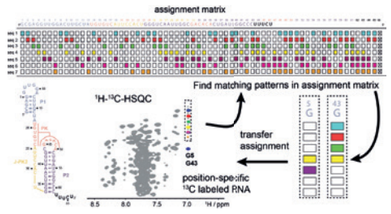


Figure 1. Fast and reliable RNA resonance assignment by position specific stable isotope labeling via RNA solid phase synthesis.

>> Goal: To characterize structure and functional dynamics of biologically relevant RNAs and DNAs by solution NMR spectroscopy.

>> Background: Nucleic acids play important biological roles. For a comprehensive understanding of an RNA/DNA's cellular function, a high-resolution 3D structure is needed. In recent years it has become more and more apparent that besides the structure of the most stable low free energy state, biomolecules undergo interconversions to called excited states - high free energy states, which are populated to a low extent. These minor states, however, play important roles in the RNA/DNA function and are involved in ligand recognition or ribozyme catalysis. NMR spectroscopy has proven to be a highly effective tool to investigate the structure and to characterize the kinetic signature of these excited states. By combining advanced (oligo)nucleotide synthesis methods to introduce NMR active labels and solution NMR spectroscopy we can characterize the ground state structures but also the excited state of RNA/DNA with unprecedented resolution.

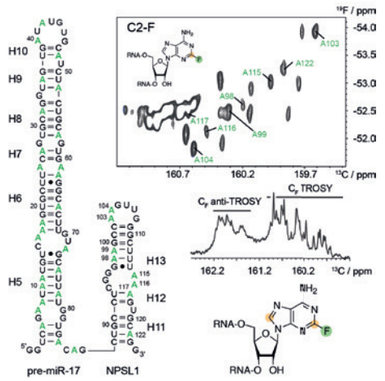


Figure 2. New labeling technique for large RNAs capitalizing on 2-^{19}F-2-^{13}C-adenosine labeling.

>> Research highlights and outlook: We recently introduced a rapid RNA assignment approach by combining chemical and enzymatic ^{13}C and ^{15}N stable isotope labeling. We exemplify the assignment strategy for imino N1H1 purine and N3H3 pyrimidine and aromatic C6H6 pyrimidine, C8H8 purine and C2H2 adenine resonances for a large non-coding RNA comprising 66 nucleotides. The assignment strategy is based on position specific labeling by chemical solid phase synthesis and dilute stable isotope ^{13}C/^{15}N-labeling by mixing labeled and commercially available unlabeled RNA phosphoramidites. The approach is fast with a total NMR measurement time of only 22 h and also competitive in terms of costs as compared to the standard methodology relying on in vitro transcription using ^{2}H, ^{15}N and ^{13}C/^{15}N uniformly labeled ribonucleotide triphosphates. In collaboration with Mark Glover (Alberta, Canada), Xavier Chapentier (Lyon, France) and Martin Tollinger (Innsbruck, Austria) we also investigated the structural basis for RNA recognition by ProQ/FinO proteins, through the crystal structure of the ProQ/FinO domain of the *Legionella pneumophila* DNA uptake regulator, RocC, bound to the transcriptional terminator of its primary partner, the sRNA RocR. The structure reveals specific recognition of the 3' nucleotide of the terminator by a conserved pocket involving a β-turn-α-helix motif, while the hairpin portion of the terminator is recognized by a conserved α-helical N-cap motif. Structure-guided mutagenesis reveals key RNA contact residues that are critical for RocC/RocR to repress the uptake of environmental DNA in *L. pneumophila*. Structural analysis and RNA binding studies reveal that other ProQ/FinO domains also recognize related transcriptional terminators with different specificities for the length of the 3' ssRNA tail.

Large RNAs are central to cellular functions, but characterizing such RNAs remains challenging by solution NMR. We introduced two labeling technologies based on [2-^{19}F, 2-^{13}C]-adenosine, which allow the incorporation of aromatic ^{19}F-^{13}C spin pairs. The labels when coupled with the transverse relaxation optimized spectroscopy (TROSY) enable us to probe RNAs comprising up to 124 nucleotides.

>> Research Grants

FWF P3277, FWF P34370, FWF I5287, FWF SFB RNADeco F8016, Esprit PostDoc scholarship (to Filip Sebest)

>> Coworkers

Raphael Plangger, Filip Sebest (Postdocs), Andreas Erharter, Stefan Hilber, David Glänzer, Fabian Juen, Alessandro Marotto, Lisa Ruetz (PhD students), Alen Reka, Marc Reier, Maximilian Mühlbauer (diploma students)

Bioanalytics & Intermediary Metabolism: Hub Molecule Metabolism and Molecular Signaling

Marcel Kwiatkowski

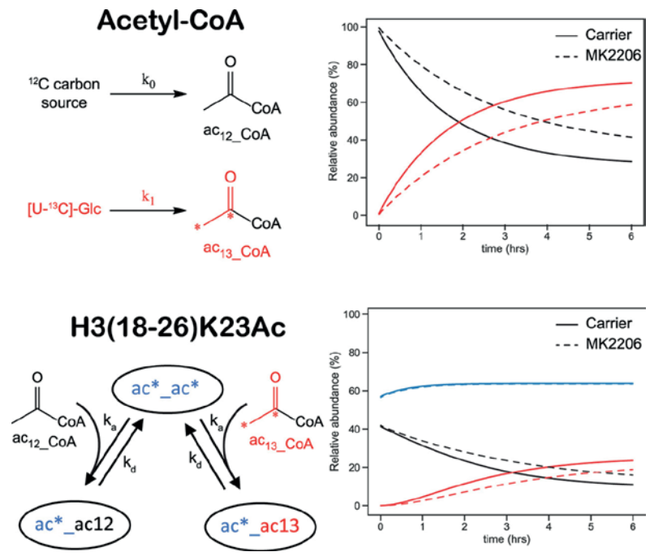
>> Department of Biochemistry

>> Goal: Our research aims to elucidate the molecular mechanisms at the interface of metabolism and signaling within the contexts of cellular homeostasis, systems biology, epigenetics, cancer, and metabolic diseases. Our group specializes in mass spectrometry-based cross-omics. This includes cutting-edge proteomics, metabolomics, and metabolic flux analysis. We combine these techniques with computational modelling and cell biology to study the regulatory interplay between cellular metabolism and protein modifications.

>> Background: Biological systems inherently seek and maintain homeostasis, a process in which cellular metabolism and epigenetic signaling play important roles. Hub molecules such as acetyl-CoA, NAD, SAM, and ATP are pivotal in cellular metabolism and signaling. These cofactors act as direct substrates for protein modifications, such as ribosylation, phosphorylation, acylation, and methylation. They are also involved in enzymatic diacylation (NAD) and demethylation (FAD) reactions. Alterations in cofactor metabolism and in the modification of proteins and histones are associated with diseases such as cancer, neurological disorders, inflammatory diseases, and metabolic diseases. A more profound understanding of the connection between intracellular hub molecule metabolism and subcellular signaling would significantly improve our molecular understanding of cell homeostasis. This would substantially impact pathologies associated with changes in hub molecule metabolism and cellular and epigenetic signaling.

>> Research highlights and outlook: To study biochemical effects at the metabolic (hub molecules) and signaling (protein modifications) levels and to integrate these levels, we have developed a simultaneous proteo-metabolome liquid-liquid extraction (SPM-LLE) approach that permits the simultaneous quantitative analysis of the metabolome including cofactors and hub molecules, and the proteome, including histone and histone modifications [van Pijkeren et al. Journal of Proteome Research, 2023], as well as protein phosphorylation [Zhang et al. Analytical Chemistry, 2022]. For translational biomarker studies, we have developed an automated and validated workflow for the isolation and absolute quantification of canonical and non-canonical amino acids and tryptophane metabolites from serum and plasma by dual U(H)PLC-MS

Figure 1: Schematic representation of the ordinary differential equations (ODE) system used to calculate the reaction rates for acetyl-CoA synthesis, as well as H3K23 acetylation and deacetylation reactions (left). Metabolic label incorporation and label loss of acetyl-CoA and acetylated H3(18–26) species fitted with ODEs (right).



[Kipura & Hotze et al. Metabolites, 2024]. To investigate the regulatory interplay between hub molecule turnover (acetyl-CoA) and epigenetic signaling (histone acetylation), we have developed a bioanalytical systems "proteo-metabo-fluxomics" approach [Egger et al. Molecular Metabolism, 2024]. We have demonstrated that our Proteo-Metabo-Flux approach allowed to determine acetyl-CoA synthesis rates and site-specific histone acetylation and deacetylation reaction rate constants. Moreover, our findings demonstrate that without the integration of acetyl-CoA and histone acetylation dynamics, the metabolic alterations induced by AKT inhibition would have been erroneously interpreted as changes in histone acetylation dynamics rather than alterations in the metabolic flux from glucose into acetyl-CoA. Our Proteo-Metabo-Flux approach was able to differentiate between these two processes. We are currently investigating subcellular hub molecule pools, their turnover (acyl-CoAs, NAD, and SAM), and their interconnection with subcellular protein and histone modification dynamics.

>> Research Grants

EU HORIZON-MSCA-DN (No: 101168783, 2025-2028), ACIB/FFG (No: 98202, 2024-2026), Tyrolian Science Fund (F.51214, 2025-2028; F.50539, 2024-2026; F.18903, 2021-2023), OeAW (2023-2024), Early Stage Funding UIBK (2020-2023)

>> Coworkers

Bernhard Sprenger (postdoc), Christina Kröß (postdoc); Tobias Kipura, Raphael Lindner, Anna-Sophia Egger (Ph.D. students); Aaron Prowatke, Anna Tichy, Nick Sartison, Verena Baumgartner, Laurin Köllenberger (master students), Madlen Hotze (lab head), Anja Reintjes (technician)

Antibody dynamics and biomolecular recognition

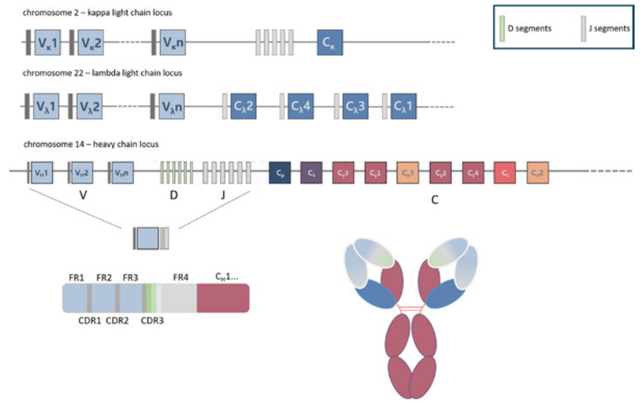
Klaus R. Liedl

>> Department of General, Inorganic and Theoretical Chemistry

>> Goal: The focus of our work lies in uncovering how interfacial hydration and domain dynamics shape heavy-light chain pairing in antibodies and influence their stability, with the long-term objective of guiding the rational design of developable therapeutic antibodies.

>> Background: Proteins are inherently flexible and exist in dynamic ensembles rather than static conformations. This is especially relevant for antibodies, where the variable domains (Fv) are responsible for antigen recognition and can adopt multiple paratope states. Static structural models often fail to capture the complexity of antibody behavior, particularly the interdomain motions and solvent rearrangements. Molecular dynamics simulations and enhanced sampling methods have become essential tools to investigate the flexibility, thermodynamics, and hydration of antibody interfaces.

>> Research highlights and outlook: Our research highlights the dynamic nature of antibody variable (Fv) domains, with a particular focus on how different germline pairings influence interfacial hydration and structural stability. Antibodies do not exist as single static entities but rather as conformational ensembles, where paratope states—defined by the arrangement of CDR loops and VH–VL domain orientations—interconvert over micro- to millisecond timescales. These transitions are modulated not only by sequence but also by solvent dynamics at the interface.



Analysis of the Observed Antibody Space (OAS) and Structural Antibody Database (SAbDab) revealed non-random pairing patterns between heavy and light chain germlines. Certain germline combinations (e.g., IGHV3-23/IGKV1-39) exhibit low interfacial hydration and higher thermal stability, whereas others (e.g., IGHV3-53/IGKV4-1) display more hydrated interfaces and lower melting temperatures. These findings suggest that the hydration state is a critical factor in pairing preference and stability.

We use molecular dynamics simulations, enhanced sampling, Markov state models, and Grid Inhomogeneous Solvation Theory to dissect how hydration hotspots, gating residues, and interfacial channel geometries vary across germlines. This approach allows us to define the physical principles underlying pairing selectivity and offers predictive power for selecting germline combinations that optimize antibody developability and biophysical performance.

>> Research Grants

FWF P34518, FWF DOC178, EU Horizon 2020 Marie Skłodowska-Curie grant No. 847681, EU Horizon 2020 Marie Skłodowska-Curie grant No. 847476, Boehringer Ingelheim, Roche

>> Coworkers

Bernhard Rupp, Christofer Tautermann, János M. Varga (Priv. Doz.), Sebastiaan Werten, Dennis Dinu, Xuechen Tang, Clarissa Seidler (postdoc), Martin Heiss, Valentin Hörschinger, Katharina Kröll, Jonas Schlagin, Vera Spanke, Alesia Yakimchyk (Ph.D. students), Dominik Hörtnagel, Lukas Meinschad, Leonardo Pedri, Adrian Senn, Christoph Teufl

Chemical Methodology and Synthesis of Natural Products

Thomas Magauer

>> Department of Organic Chemistry

>> Goal: To develop expedient synthetic access to biologically active natural products.

>> Background: Our research program is driven by natural products in the broadest sense, encompassing method development, total synthesis, and mechanistic studies. Natural products have served as a source of inspiration for scientists for over a century. The intricate molecular framework has proven to be an indispensable source of innovative ideas, powerful chemical transformations, and important biological insights. We strive for the discovery and development of efficient transformations for synthetic chemistry with the goal to produce functionalized compounds and biologically active molecules with high efficiency. As an advocate of basic research, I encourage my group to look for the unexpected and explore ideas beyond the state of the art.

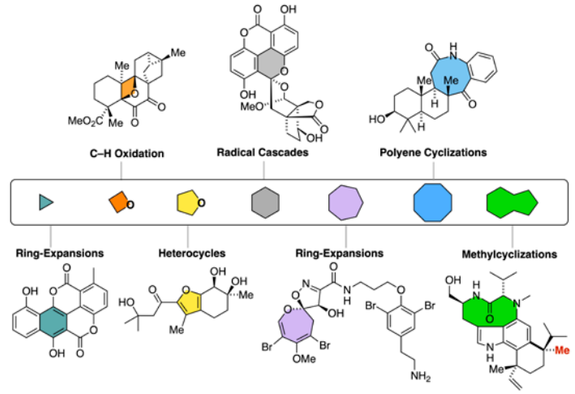


Figure 1 Three-dimensional natural products can offer several advantages over fully synthetic, flat molecules. However, the structural complexity of many natural products has often prevented their use as medicines. As a result, most small molecules developed by the pharmaceutical industry have a high proportion of sp^2-carbons. We see this as a motivation to think about innovative retrosynthetic disconnections. The future goal is to discover highly efficient synthetic methods and to enable faster and more efficient routes to target molecules.

>> Research Grants

ERC Consolidator Grant “CRAFTMOL” 101000060; FWF PAT1457923; FWF P 33894-N

>> Coworkers

Daniel Atzl (MSc), Tessa Trieda (MSc), Sebastian Schaar (PhD), Thomas Hintner (PhD), Nora Sechet (PhD), Julian Lichtenegger (PhD), Alex Mühlsteiger (PhD), Nicolas Müller (PhD), Immanuel Planger (PhD), Aldo Tancredi (PhD), Elias Schmidhammer (PhD), Jan Paciorek (PhD), Jasmin Ferreira (PhD), Dinmukhammed Slyamayev (PhD), Adrien Merviel (PhD), Michael Badart (Postdoc), Gerhard Scherzer (Technician)

>> Research highlights and outlook: We developed ring-expansion reactions of cyclopropanes (now referred to as “carbon-editing”) to synthesize polyfunctionalized (hetero)arenes (Figure 1). Our work on antifeedant natural products led to our investigations of non-directed C–H oxidation to polyoxygenated terpenoids. (Mero)terpenoids have played a crucial role for reactions at high-pressure (14 kbar), directing us towards heterocycles and the elucidation of reaction mechanisms by computational methods. In addition, these natural products have fueled our program on radical cascade reactions and polyene cyclizations. For the latter we were able to realize powerful cyclization reactions of heteroatom substituted carbon chains involving unprecedent termination steps, providing rapid access to complex molecular libraries. This recently led to the discovery of conditions that mimic naturally occurring bifunctional methyltransferases.

Developmental Biology

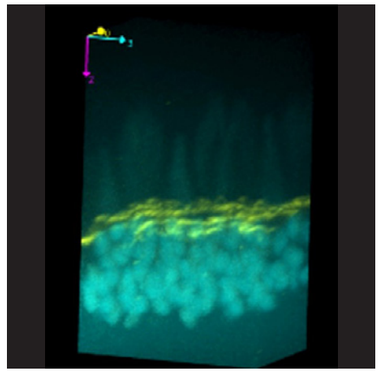
Dirk Meyer and Robin Kimmel

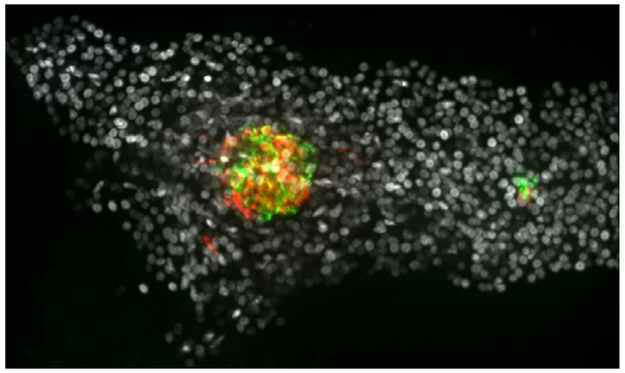
>> Department of Molecular Biology

>> Goal: To understand molecular mechanisms underlying fate specification, differentiation, migration and maturation, with a focus on vertebrate gastrulation and the formation of pancreatic islet cells. We further aim to elucidate endocrine islet function and related disease mechanisms.

>> Background: Establishment and functionality of endodermal organs such as the pancreas requires a still poorly understood coordination between proliferation, migration, differentiation and maturation. Disturbance of pancreas formation can lead to insufficient cell numbers and perturbed function, which then disrupts organism metabolism. In our research we apply genetic, molecular and *in vivo* imaging approaches in zebrafish and human stem cells to study (1) the transcription network of early embryonic germ layer induction, (2) the genetic and molecular programs regulating beta-cell and islet formation during embryonic development and regeneration and (3) to understand the underlying molecular and physiological defects of Diabetes associated risk factors.

>> Research highlights and outlook: Islet development and function: We have demonstrated that motile endocrine cells depend on PI3K and GPCR signaling during islet assembly. With newly developed tools for single cell analysis of endocrine cell dynamics and physiology, we are exploring paracrine signals and ion fluxes that regulate insulin secretion, and cell-cell communication that impacts islet morphogenesis. Related studies use novel zebrafish mutants and engineered stem cells to uncover the genetic program regulating vertebrate germ layer formation and differentiation of pancreatic islet cells.





>> Research Grants

FWF 10.55776/PAT7848524, FWF 10.55776/P35746, FWF 0.55776/P31883, FWF PhD Programme 10.55776/DOC178: CavX – Calcium channels in excitable cells
H2020 Research and Innovation Programme, No. 899612 (SWIMMOT Project), EU H2020 Doctoral Programme "ARDRE - Ageing, Regeneration, and Drug Research"

>> Coworkers

Patrick Fischert, Dominik Regele, Nicole Schmitner (Postdocs), Pauline Bicker, Rosalie Dittrich, Fabian Rabensteiner, Divya Sakthivel, Marc Sathianathan, Nargess Shahbazi, Melanie Zott (Ph.D. Students); Nadine Alge, Ferdinand Loeffler, Lara Schatt (Master Students); Sonja Töchterle, Thomas Walder, Dzenana Tufegdzic (Technician)

Diabetes-related studies: Together with international collaborators, we characterized novel requirements of Diabetes-associated ion-channels in glucose induced beta-cell excitability. Furthermore, using our diabetic zebrafish models to investigate the long term impact of disrupted glucose homeostasis, we examine mechanisms underlying progression of retinal vascular and neural pathologies that resemble human diabetic retinopathy. Studies underway aim to clarify involvement of candidate factors identified from transcriptomic analyses. In other work, we investigated how the enzyme glucokinase contributes to organism glucose homeostasis and how glucokinase modulation may be harnessed for treatment of diabetes. In the EU-funded project SWIMMOT, advanced nanoparticle-based contrast agents developed for high resolution *in vivo* imaging are used to address biomedical questions using our zebrafish disease models.

Synthesis, structure, and function of non-coding RNAs

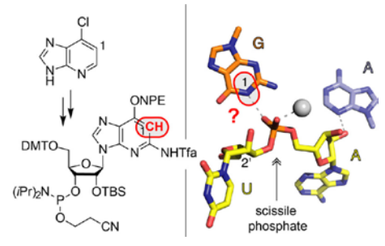
Ronald Micura

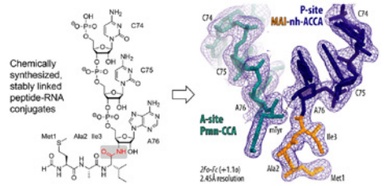
>> Department of Organic Chemistry

>> Goal: To obtain an integrated understanding of RNA modification and RNA mediated regulation and catalysis.

>> Background: For many years it was believed that there were only a small number of non-protein-coding RNAs (ncRNAs) and that they (tRNAs, rRNAs, spliceosomal RNAs) were involved primarily in assembling the predominant protein macromolecules. Even large RNA classes, such as snoRNAs and microRNAs, remained undetected. In recent years, it became apparent that ncRNAs are numerous and that their cellular functions – on their own or in complex with proteins – are diverse and important. Our lab aims at a comprehensive molecular understanding of cellular processes involving ncRNAs, in particular of gene regulation by riboswitches but also of traditional ncRNAs such as encountered during ribosomal translation. Our lab has a major focus on the *chemical synthesis of RNA* allowing the introduction of site-specific modifications, naturally occurring and artificial ones. This enables us to evaluate their structure and function by a great diversity of chemical and biophysical methods, with a focus on chemical and biochemical probing techniques, fluorescence spectroscopy (including single molecule imaging), NMR spectroscopy, and X-ray crystallography.

>> Research highlights and outlook: Atomic mutagenesis is the key to advance our understanding of RNA recognition and RNA catalysis. To this end, deazanucleosides are utilized to evaluate the participation of specific atoms in these processes. One of the remaining challenges is access to RNA with 1-deazaguanosine (c^1G). We developed the synthesis of this nucleoside and its phosphoramidite, allowing first time access to c^1G-modified RNA. Thermodynamic analyses revealed the base pairing parameters for c^1G-modified RNA. Furthermore, by NMR spectroscopy, a c^1G-triggered switch of Watson-Crick into Hoogsteen pairing in HIV-2TAR RNA was identified. Additionally, using X-ray structure analysis, a guanine–phosphate backbone interaction affecting RNA fold stability was characterized, and finally, the critical impact of an active-site guanine in twister ribozyme on the phosphodiester cleavage was revealed. Taken together, these studies provided the synthetic basis for c^1G-modified RNA and demonstrated the power of the completed deazanucleoside toolbox for RNA atomic mutagenesis needed to achieve in-depth understanding of RNA recognition and catalysis.





Researchers have achieved much progress in characterizing ribosomal translation at the molecular level; an impressive number of high-resolution structures of different functional and inhibited states of the ribosome are available. These structures have significantly contributed to our understanding of how the ribosome interacts with its key substrates, namely, mRNA, tRNAs, and translation factors. In contrast, much less is known about the mechanisms of how small molecules, especially antibiotics, affect ribosomal protein synthesis. This mainly concerns the structural basis of small molecule–NPET interference with cotranslational protein folding and the regulation of protein synthesis. Progress in this field is hampered by the fact that during the preparation of ribosome complexes for structural studies (i.e., X-ray crystallography, cryoEM) the peptidyl-tRNAs are unstable and become hydrolyzed. A solution to this problem are hydrolysis-resistant mimics of peptidyl-tRNAs. We developed modular approaches for the generation of such analogs that combine (i) RNA and peptide solid-phase synthesis on 3′-aminoacylamino-adenosine resins, (ii) native chemical ligations and Staudinger ligations, (iii) tailoring of tRNAs by the selective cleavage of natural native tRNAs with DNAzymes followed by reassembly with enzymatic ligation to synthetic peptidyl-RNA fragments, and (iv) enzymatic tailing and cysteine charging of the tRNA to obtain modified CCA termini of a tRNA that are chemically ligated to the peptide moiety of interest. With this arsenal of tools, any desired sequence of a stably linked peptidyl-tRNA mimic is accessible. These synthetic conjugates allowed many applications that have shed new light on the molecular mechanisms underlying the context-specific activity of ribosome-targeting antibiotics, ribosome-dependent incorporation of multiple consecutive proline residues, the incorporation of D-amino acids, and tRNA mischarging.

>> Research Grants

FWF (P31691, SFB RNA-Deco F8011, ESP314), FFG (858017 – West-Austrian BioNMR), WWTF (LS17-003)

>> Coworkers

Karolina Bartosik, Przemyslaw Wanat (postdoc); Maximilian Himmelstoß, Sarah Moreno, Stefan Mair, Laurin Flemmich, Michaela Egger, Raphael Bereiter, Julia Thaler, Clemens Eichler, Anna Rázková, Christoph Mitteregger, Marco Oberlechner, Jonas Kottersteger, Alexander Pichler (Ph.D.); Daniel Fellner (technician)

Pharmacognosy – traditional knowledge meets the 21st century

Simone Moser, Hermann Stuppner, and Markus Ganzera

>> Department of Pharmacy, Pharmacognosy Section

>> Goal: To rationalize the (medical) use of natural products from diverse organisms (plants, fungi, algae) by studying their constituents (focus: isolation and structural elucidation), quantitative occurrence (focus: analytics) and activity (focus: bioassays).

>> Background: Natural products were and still are the primary source of pharmaceuticals, whether they are used in their native form or serve as lead structures for further optimization. Yet, to meaningfully untap these versatile and mostly still unknown resources, a multidisciplinary and state-of-the-art approach is needed. It is thus not surprising that the well-established concepts of activity-guided isolation and chromatography were augmented by innovative approaches in the recent past. They include isolation techniques like Fast Centrifugal Partition Chromatography (FCPC), Supercritical Fluid Chromatography (SFC) for analysis, or the visualization of large data-sets by computational methods such as Feature-Based Molecular Networking (FBMN). All of them have been implemented at the Institute of Pharmacy / Pharmacognosy and provide the backbone of ongoing phytochemical research, which was significantly strengthened by installing a fully equipped cell culture laboratory. The performed studies on the protein-protein as well as small molecule-protein-interactions using a yeast based system enable a comprehensive workflow from plant to the target identification of bioactive compounds. Clearly, the extension of classical pharmacognosy towards pharmaceutical biology is in progress.

Cover Art of Keil et al., Chem. Sci., 2025, 16, 1684-1695, DOI https://doi.org/10.1039/D4SC06441K

>> Research highlights and outlook: One current research focus was the development of liquid-liquid separation methods, such as FCPC (fig. 1). It utilizes immiscible liquids at equilibrium, forming a two-phase system. The separation of the compounds is achieved according to their partition coefficients and thus FCPC represents an orthogonal technique to the more common approaches employing a solid stationary phase. By using "green solvents", this technique is also environmentally friendly. The application range is rather wide, as evidenced by successfully conducted projects in-house. They range from water free two-layer systems for the separation of rather lipophilic compounds (paraconic acids) to very polar substances using water/salt systems (mycosporine-like amino acids, MAAs). Other applications include the separation of poorly soluble compounds like anthraquinones or natural products, which show a strong interaction with solid phases like the alkaloids in *Chelidonium majus*. However, FCPC is also useful for the purification of reaction mixtures, as evidenced by the separation of derivatives of 2-amino-3H-phenoxazin-3-one.

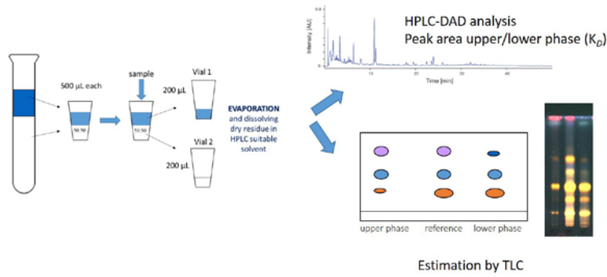


Figure 1: Workflow for the rational development of CPC-systems using the shake-flask method with KD value estimation by HPLC-DAD analysis or TLC visualization.

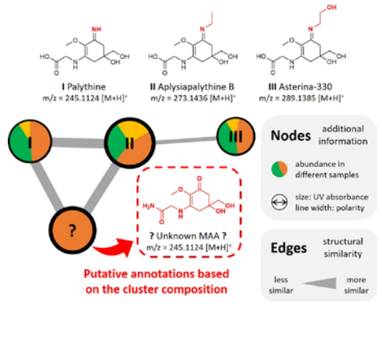


Figure 2: Simplified representation of a cluster consisting of three structurally related MAAs and one unknown compound, including an explanation of commonly used visual attributes (information layers) used in the FBMN approach.

The FWF project "UVision" investigates the occurrence and distribution of MAAs, a group of natural compounds often referred to as environmentally friendly sunscreens. In cooperation with the University of Rostock, the eyes of 39 fish species were examined for their MAA content using HPLC-DAD. Several species exhibited amounts similar to those of intertidal seaweeds, the main producers of MAAs. The identification of novel MAAs, however, requires a combination of state-of-the-art separation techniques, mass spectrometry, and bioinformatics. Feature-based molecular networking, a visualization approach for UHPLC-HRMS/MS data in which compounds are arranged into clusters of structurally similar molecules, has proven to be highly promising in this regard (fig. 2). In a proof-of-concept study, FBMN was employed on a set of different algae and enabled the annotation of several yet unknown MAA-like metabolites in *Bostrychia scorpioides*. This led to the subsequent isolation and identification of the bostrychines G-L.

With chlorophyll and the chlorophyll related phyllobilins, a new research field has been established at the Department of Pharmacognosy. Together with the expertise in analytical chemistry and isolation techniques applied to the purification of tetrapyrrolic pigments covering a broad polarity range, we can provide and enable studies on these challenging natural products (see cover art). Interestingly, the concentration of linear tetrapyrroles increases during the storage of vegetables and fruits, yet their presence in medicinal plants has been overlooked until now. Our research aims to analyse the 'phyllobilin fingerprint' in such matrices, as well as to investigate their pharmacokinetic properties. This is especially relevant as previous studies indicate that phyllobilins remain stable in digestive fluids and are not metabolized by hepatic enzymes. Research projects in the future will focus on their occurrence in medicinal plants as well as bioavailability and potential physiological effects.

>> Research Grants

FWF ZFI061220, Aurora European University Alliance P7400-038-013, FWF ZFP370010, LFUI ESF WS740103, ZAP740047, LFUI FZ Berglandwirtschaft P7400-043-011, VasCage P7400-042-011, LFUI IRO P7400-038-012, FWF ZFI058670, TWF P7400-035-011, LFUI ESF WS740102, OeAD P7400-028-012, EU - Horizon 2020, COFUND P1972-013-012, EUREGIO ZFIPN001190, FWF ZFP371630, TWF ZAP740041

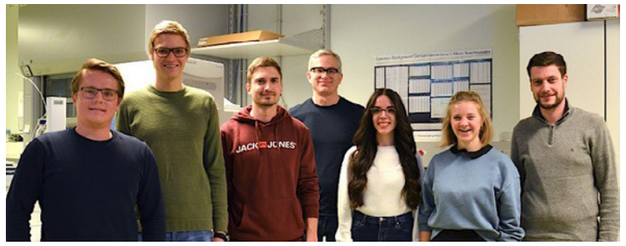
>> Coworkers

Cornelia Karg, Stefan Schwaiger, Bianka Siewert, Sonja Sturm, Birgit Waltenberger (senior scientists); Mostafa Alilou, Clara Bertel, Fabian J. Hammerle, Umesh Kumar, Javad Mottaghipisheh, Francisco Javier Rodríguez Mejías, Lisa Schwaiger (postdocs); Minh Bui Hoang, Ana Drmic, Christian Elvert, Johannes Fiala, Mark James Horgan, Sofia Karavergou, Loc Le Xuan, Yun Liu, Elahe Mirzaei Moghadam, Domenic Mittas, Sophie Schwarzkopf, Angelika Seeber, Jonas Stehlin, Eduardo Villicana Gonzalez, Michael J. Zwerger (PhD students); Elyas Ahmadi, Sonja Beiler, Clemens Bauernfeind, Lisa Gstrein (technicians)

Chemistry, chemical and structural biology of the pigments of life

Bernhard Kräutler and Thomas Müller

>> Department of Organic Chemistry



>> Goal: To gain knowledge on the chemistry, biological roles and bio-molecular interactions of critical porphyrinoid and other metabolites, and to apply this in biology and medicine.

>> Background: A large part of our research concerns the porphyrinoid 'pigments of life', which have crucial and diverse roles in cells, e.g. as cofactors in enzymes, in biological processes driven by solar light and as exceptional gene-regulating metabolites. They comprise heme, chlorophyll, corrinoids and linear tetrapyrroles, which result from breakdown of heme and of chlorophyll. Porphyrinoids owe their roles in Nature to their unique molecular properties. Some of their basic structures are assumed to have pre-biotic origin. Frequently they are functional complements as coenzymes to proteins, or (less well known) as structuring and regulating ligands of proteins and noncoding RNA, e.g. in B_{12}-riboswitches. Our approach is dedicated to gaining chemistry-based insights into the biological roles of essential porphyrinoids and other metabolites, as well as at exploring their effects in important cellular processes.

>> Research highlights and outlook: We have been contributing to the chemistry of vitamin B_{12}-derivatives, in particular, as part of our recent program on 'antivitamins B_{12}', metabolically inert structural B_{12}-mimics (see Eschenmoser-Lecture 2023). This research will help us learn more about mechanisms of B_{12}-dependent metabolic processes in microorganisms, animals and humans, as well as in looking at still enigmatic effects of B_{12}-deficiency by B_{12}-chemical biological approaches. In this context, we have developed a synthetic approach towards a group of B_{12}-mimics that contain transition metals other than cobalt, the specific metal center of the natural B_{12}-derivatives. A combination of biological and chemical total synthesis was developed for this purpose, furnishing the 'mother' ligand of vitamin B_{12}, hydrogenobyric acid, as key component. This 'contracted' helical corrin macrocycle has an intriguing capacity for binding cobalt and other transition metals in activated, or 'entatic' states. As new examples diamagnetic rhodium-analogues of the natural B_{12}-cofactors were synthesized, their structures scrutinized by X-ray analysis and their interactions with biological macromolecules examined (Figure 1).

Our labs have also pioneered studies on the structure and chemistry of chlorophyll catabolites (phyllobilins) from senescent ferns, ginkgo and gymnosperms. We have elucidated the structures of novel chlorophyll-degradation products. These represent unprecedented molecular reporters for the evolution of chlorophyll degradation in the Paleozoic (Figure 2). Furthermore, we developed 3D printed immobilized enzyme microreactors (μIMERs) for protein analysis and established an advanced motion tracking for interactive mass spectrometry imaging (Figure 3).

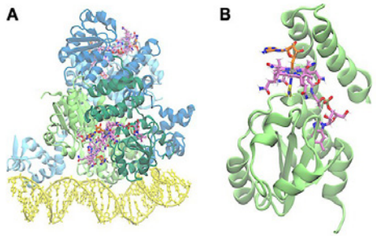


Figure 1. Bacterial photoregulation by coenzyme B_{12}. The sequence-specifically DNA-binding complex of four CarH-proteins (panel A). Each of these binds coenzyme B_{12} or its rhodium-analogue, designed as anti-photoregulatory ligand, blocking the transcription of proteins involved in the biosynthesis of carotenoids; panel B: calculated structure of the protein CarH binding the Rh-analogue of coenzyme B_{12} (see R. Perez-Castano et al., 2024).

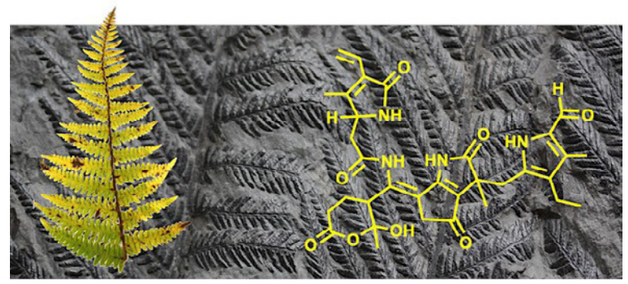


Figure 2. New types of phyllobilins have been discovered in ferns, which are considered to be molecular reporters for the development of chlorophyll degradation in the palaeozoic era (see T. Erhart et al. 2024).

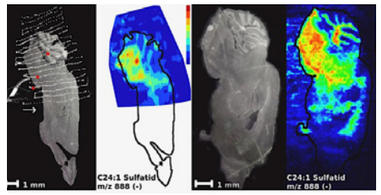


Figure 3. Comparison of DESI-Interactive Mass Spectrometry Imaging (left) and conventional DESI-Mass Spectrometry Imaging (right) of mouse brain tissues in negative ion mode.

>> Research Grants

FWF P-33059

>> Coworkers

M. Wiedemair, A. Pandey (postdocs), C. Nadegger, T. Rainer (Ph.D. students), C. Messner, A. Ploner, D. Sessa, B. Steger (master students)

Cell physiology and environmental stress

Bernd Pelster, Adolf Sandbichler, and Thorsten Schwerte

>> Department of Zoology

>> Goal: Our research aims at the analysis of molecular and structural mechanisms as well as genetic control pathways of physiological phenomena.

>> Background: The adaptation of animals to changing environmental conditions includes adaptations at the behavioral, cellular and molecular level in order to maintain homeostasis of energy metabolism, ion regulation and acid base balance. Changing oxygen partial pressures, variable light regimes or temperatures, for example, are readily perceived by animals of different developmental stage. In our work we focus on the large-scale changes in the overall gene expression and behavioral patterns induced by these environmental perturbations, typically resulting in characteristic modifications in metabolic defense reactions, activity patterns, oxygen transport capacities and overall metabolic or ion regulatory activity. Of particular interest are the control mechanisms guiding these expression changes at the transcriptional and translational level. The sophisticated interconnection and interaction between the different regulatory pathways is addressed using appropriate invertebrate and vertebrate model animals. The data, obtained at the molecular, cellular and organismic level, are discussed with respect to the possible adaptational benefit for the whole organism.

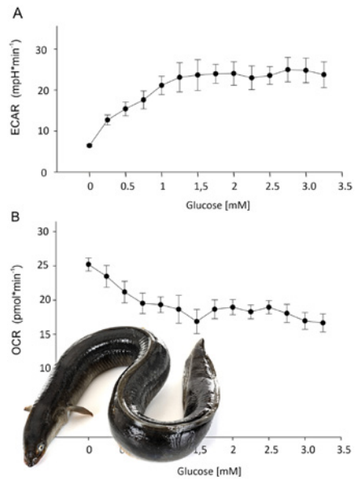


Figure 1: Acid secretion (ECAR) (**A**) and oxygen uptake (OCR) (**B**) in relation to increasing glucose concentrations in isolated gas gland cells of the European eel *Anguilla anguilla*. ECAR rapidly increased with increasing glucose concentrations and leveled off at glucose concentrations above 1.5 mmol l^{-1}. OCR decreased with increasing glucose concentrations and remained stable at concentrations above 1.5 mmol l^{-1}; $N=6$. From: Drechsel V, Schneebauer G, Sandbichler AM, Fiechtner B, Pelster B. Oxygen consumption and acid secretion in isolated gas gland cells of the European eel *Anguilla anguilla*. *Journal of Comparative Physiology B: Biochemical, Systemic, and Environmental Physiology* **192**, 447-457 (2022).

>> Research highlights and outlook: One focus of our research is the development of an innovative artificial nesting cavity designed to support bees and other pollinating insects. Utilizing advanced thermal insulation and diffusion-open materials, this patented design creates an optimal microclimate, reducing climatic stress on bee colonies. The structure effectively regulates moisture and temperature, preventing harmful condensation and promoting bee health. This innovation addresses biodiversity loss, climate change, and food security challenges by enhancing pollinator resilience and ensuring sustainable ecosystems.

In our research on cellular redox balance and hypoxic stress response, we use organelle-specific fluorescent protein sensors combined with advanced microfluidic live-cell imaging. This allows us to measure reactive oxygen species (ROS) in different organelles, such as peroxisomes or mitochondria. We investigate their role in maintaining whole-cell redox equilibrium and examine how redox changes affect cellular oxygen consumption and glycolytic metabolism.

Figure 2: Honeybee brood frame from a zero-energy beehive (patent pending) at the Institute of Zoology. The image depicts a densely populated comb with *Apis mellifera* worker bees tending to brood cells at various developmental stages. The capped cells contain pupating larvae, while uncapped cells reveal eggs and younger larvae. The hive is designed for optimal thermal regulation and minimal external energy input, promoting sustainable beekeeping practices. The beekeeper, partially visible in protective gear, is inspecting the colony for health and development.

The availability of amino acids, or their loss due to stress or disease, directly affects metabolism and consequently the formation of ROS. Our research compares these conditions in fish cells and mouse cells, aiming to describe previously unknown evolutionary changes in metabolic plasticity.

Recently, in a cooperation with the Medical University of Innsbruck, the influence of Interleukin-6 (IL-6) signaling on redox balance and metabolism in a neuronal context is being investigated. Sophisticated metabolic measurements help to study a novel non-canonical response to IL-6 that increases cellular oxygen consumption and reduces ROS.

We incorporate advanced image analysis with machine learning algorithms into our data extraction routines. With these tools we can address changes on the organismic level as well as cellular and organellar morphology at high temporal and spatial resolution in long-term time-lapse live cell imagery.

A UPLC/MS system at the Institute of Zoology enables the analysis of metabolite consumption and fate in cell culture and tissue samples exposed to various physiological drivers. This measurement technique expands and complements our expertise in metabolic analysis within the Metabolic Analysis Cluster Innsbruck (MACI).

The swimbladder is an important buoyancy aid for many fish, and epithelial gas gland cells of the swimbladder are crucial for gas secretion. Analysis of oxygen consumption and possible control mechanisms of gas gland cell activity revealed muscarinic and cAMP dependent control mechanisms of metabolic activity in these cells. Furthermore, by connecting secretory activity of gas gland cells and the role of the countercurrent system of the swimbladder, the rete mirabile, the importance of CO_2 secretion by gas gland cells and of CO_2 back-diffusion in the rete mirabile for gas secretion into the swimbladder could be demonstrated. Respiratory swimbladders typically are connected to a reduction in gill surface area, which is not only required for gas exchange, but also for ion regulation and nitrogenous waste secretion. Analysis of gas exchange and nitrogenous waste secretion in Amazonian air-breathing fish revealed an elevated contribution of urea to total nitrogen excretion.

>> Research Grants

Non-canonical redox response to neuronal Interleukin-6 signaling - NeuREDOX, Tiroler Wissenschaftsförderung, 2023-2024; Bioinspired & Generative Design with artificial intelligence. Austrian Research Promotion Agency (FFG), Innovation Camps. 2024 – 2025 https://projekte.ffg.at/projekt/5129231

>> Coworkers

Birgit Fiechtner, Bettina Peer (Technicians); Stefanie Jäger (PhD student), Anna Fleischmann, Mohamed Fathy

Development of opioid ligands with target-directed activities

Mariana Spetea

>> Department of Pharmacy, Pharmaceutical Chemistry Section

>> Goal: To perform basic and applied research in medicinal chemistry and pharmacology of the opioid system with innovative ligands targeting the opioid receptors and new mechanism-based treatment strategies for human diseases.

>> Background: The kappa-opioid receptor (KOR), a G protein-coupled receptor (GPCR) and a prominent member of the opioid receptor family, has gained increased attention to drug discovery over the recent years. The endogenous KOR is expressed in the central and peripheral nervous systems, and has a key role in modulating numerous physiological functions and neuropsychiatric behaviors. The knowledge that activation of the KOR, opposite to the mu-opioid receptor, does not produce euphoria, respiratory depression or risk of overdose has stimulated the interest in discovering drugs acting on the KOR as potential therapeutics. Differential modulation of KOR signaling (activation/inhibition) is viewed as a promising strategy for developing pharmacotherapies for various human disorders (i.e. pain, mood disorders, drug addiction and neurological diseases), where the kappa opioid system plays a central function (Figure 1A).

>> Research highlights and outlook: Central directions of our research KOR program include modulation of ligand/KOR interactions, structure-activity relationships (SAR), understanding the mechanism of opioid actions at the KOR, and the link between therapeutic effects (i.e. analgesia, epilepsy), side effects and molecular mode of action. The specific research goals include drug design and synthesis, pharmacological characterization and SAR studies of new classes of ligands selectively targeting the KOR and having distinct functional activities (agonism/partial agonism/antagonism, biased agonism). Our drug discovery strategies address structurally-diverse ligands (small molecules, and peptide and peptide analogues), and comprises screening of binding and signaling profiles at the KOR, *in vivo* broad pharmacology together with mechanistic studies.

Highlights of our recent projects include: (a) Small molecules - New classes of selective KOR ligands (Figure 1B) – (a1) Design of a series of structurally distinct, selective ligands targeting the KOR featuring a diphenethylamine scaffold (Figure 1B), and pharmacological evaluation towards potential antinociceptives with reduced liability for KOR-mediated adverse effects. The first compounds of the series, HS665 and HS666, as G protein-biased KOR agonists (Figure 1B), were used as leads

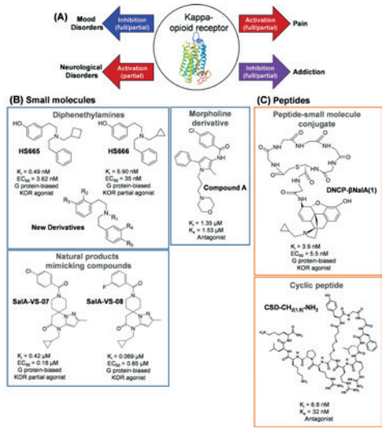


Figure 1: (A) Targeting the KOR as a new strategy for developing pharmacotherapies for various human diseases. (B) Discovery of small molecules and (C) peptides as novel, selective ligands at the KOR with distinct functional activity profile (agonism/partial agonism/antagonism, biased agonism), and potential drug candidates for the treatment of KOR-related illnesses.

>> Research Grants

FWF I2697 (with DFG, lead agency: FWF), FWF P30430, FWF P30592

>> Coworkers

Helmut Schmidhammer (Prof.); Siriwat Hongnak (postdoc); Aina-Leonor Olive Marti, Maria Guastadisegni (Ph.D. students); Nevin Sertkaya, Armin Wurzer, Alexandra Peer, Nadine Hochrainer, David Lamp, Susanne Gladen, Anja Meraner (Master students)

in the design of new libraries of derivatives to expand the SARs. We established their antinociceptive efficacy in mouse models of acute, visceral and inflammatory pain, as well as anti-epileptic effects, with less liability for KOR-mediated sedation/motor dysfunction; (a2) Discovery of novel, non-basic and selective KOR agonists via structure-based virtual screening using 3D pharmacophore models based on the binding mode of Salvinorin A (Figure 1B). SalA-VS-07 and SalA-VS-08 were identified as highly selective ligands for the KOR with a G protein-biased KOR agonist activity (Figure 1B). Both KOR ligands share a novel spiro-moiety and a non-basic scaffold, and may provide novel starting points for developing therapeutics aimed at treating pain and other pathological conditions; (a3) Discovery of a new scaffold ligand as a selective KOR antagonist (Figure 1B). Experimental *in vitro* and *in vivo* pharmacological assays, and molecular docking, molecular dynamics simulations and dynamic pharmacophore (dynophore) generation led to the identification of Compound A as a novel KOR antagonist (Figure 1B), with a structurally distinct scaffold compared to the so far known KOR ligands, and with good capability to enter the CNS. This new chemotype holds promise for chemical optimization toward the development of potential therapeutics for CNS disorders. (b) Peptides - Novel peptides and peptide analogues with selectivity for the KOR (Figure 1C) – (b1) Application of *de novo* peptide design for discovery of first-in-class peptide–small molecule conjugates as novel ligands for the KOR (Figure 1C). The designed De Novo Cyclic Peptide (DNCP)-β-naloxamine (NalA) (DNCP-NalA) (Figure 1C) displayed desired pharmacology, as it bound and activated the KOR, showed G protein-biased KOR agonism, and produced antinociception in mouse models of inflammatory pain with reduced risk for KOR-induced undesirable side effects. The computational approach to design peptides for the KOR may energize the design of next-generation therapeutics for medical applications such as pain conditions; (b2) Development of a selective cyclic peptide KOR antagonist by late-stage functionalization with cysteine staples (Figure 1C). Applying peptide cysteine stapling and the endogenous Dynorphin A as a molecular template, CSD-$CH_{2(1,8)}$-NH_2 (Figure 1C) was designed and pharmacologically established as a potent competitive and stable KOR antagonist by modulating KOR function in the CNS. This highlights the value of cysteine stapling to develop selective peptide probes to modulate central KOR function, as innovative peptide drug candidates for the treatment of KOR-related illnesses.

Through strong alliances of our research group and other scientists, novel scientific solutions and knowledge on drug discovery by targeting the KOR with recognizable innovative potential were generated. Multidisciplinary, synergistic approaches ranging from molecular *in silico* and *in vitro* levels to *in vivo* systems were used by combining computational systems with biochemical and pharmacological methods and disease animal models.

Molecular mechanisms in carcinogenesis: oncokinases and gene regulation

Eduard Stefan and Markus Hartl

>> **Department of Molecular Biology, Tyrolean Cancer Research Institute, Department of Biochemistry**

>> Goal: The aim of our research programs is to unravel the molecular mechanisms of carcinogenesis and develop innovative biotechnological approaches to be applied for basic cancer research and early stages of drug discovery. Our focus extends beyond oncokinases to include E3 ligases and still undruggable targets such as MYC and certain tumor suppressor proteins.

>> Background: Kinases are molecular switches which play crucial roles in cellular signaling pathways, regulating processes such as cell proliferation, survival, and differentiation. Our lab has traditionally focused on compartmentalized kinase signaling pathways, particularly those involving PKA, RAF, MEK, and RIPK downstream of receptor pathways. Recently, our research has expanded to explore the functions of E3 ubiquitin ligases and their interactions with tumor suppressor proteins in cancer development and progression. Transcriptional regulators are nuclear end points of kinase signaling and often aberrantly activated in cancer cells. One of these oncogenic transcription factors is MYC representing a major driver in human tumors.

>> Research highlights and outlook: Recently we have made significant progress in understanding cancer cell biology with the hope to be used for developing innovative approaches for drug discovery (Figure 1). First, Torres-Quesada *et al*. demonstrated the critical influence of physiological cell culture media on mitochondrial bioenergetics and drug sensitivity in cancer models, emphasizing the importance of cellular microenvironments in cancer research and drug development. Building on this, Feichtner *et al*. and Fleischmann *et al*. advanced novel methods for tracking mutation and drug-driven alterations of oncokinase conformations. This work complements the research by Kugler *et al*., published in eLife, which further delved into the structural dynamics of kinases. Together, these studies provide a deeper understanding of how genetic mutations, binary protein interactions and therapeutic interventions affect oncokinase conformations. In these lines in 2022, KinCon biolabs, a University of Innsbruck spin-off has been founded

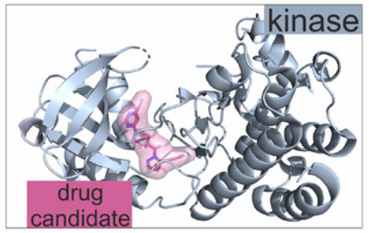


Figure 1: Shown is the protein structure of a protein kinase (grey) in complex with a kinase inhibitor (drug candidate; in red/pink).

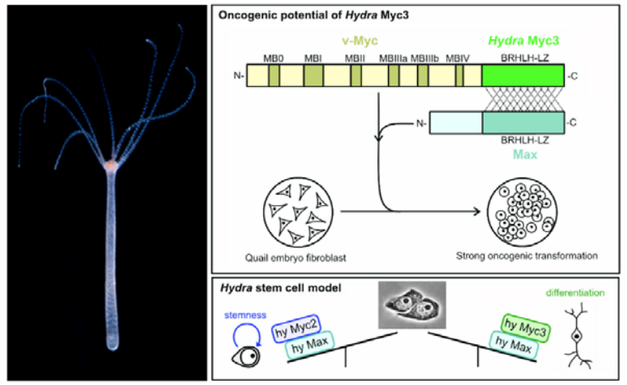


Figure 2: Structure and oncogenic function of the Myc3 protein from the freshwater polyp *Hydra*. Under physiological conditions the Myc2/Max dimer maintains stemness whereas the Myc3/Max dimer promotes differentiation.

>> Research Grants

FFG industrial PhD (2024-2027), Dr. Martin Steinmeyer Foundation (TKFI, 2024-2025), Austrian Science Fund ZFI054060 (co-applicant 2021-2025), Austrian Science Fund P35159 (2021-2025)

FFG Bridge 'MitoKin' (2020-2023), Austrian Science Fund P32960 (2020-2023), FFG Spin-off Fellowship (2019-2022), Austrian Science Fund P30441 (2018-2022), Austrian Science Fund P33662 (2020-2026), Early Stage Funding UIBK (2024-2025), OeAD P7120-024-011 (2024-2025)

>> Coworkers

Andreas Feichtner (postdoc); Valentina Kugler, Selina Schwaighofer, Jakob Fleischmann, Alexandra Fritz, Sophie Strich, Leonie Weber, Lea Timpen (Ph.D. students); Rafael Span, David Demmel, Nesin Ayhan (master students), Katharina Reinecke, Philippine Scoliège (Erasmus students), Andrea Raffeiner (lab manager), Kane Puglisi (technician)

for extending and applying a patented target-protein engagement technology to enable or accelerate the identification of new types of more efficient drug candidates.

The gene regulator MYC is evolutionary conserved in early metazoan organisms and studying these ancient molecules in the context of oncogenic transformation and cell differentiation is also relevant for human cancer. In an interdisciplinary study involving several CMBI-associated institutes we have characterized multiple MYC orthologs from the freshwater polyp *Hydra* and discovered a high intrinsic oncogenic potential of the newly identified *Hydra* Myc3 protein (Lechable *et al*., 2023) (Figure 2). Furthermore, we continued on our studies on the *BASP1* gene, a negative transcriptional target of MYC, whose protein product BASP1 interferes with MYC-induced oncogenicity. This MYC target was also used as a template to develop novel chemically modified siRNAs (Moreno *et al*., 2022; Eichler *et al*., 2023).

Cell signaling in chronic CNS disorders

Nicolas Singewald and Jörg Striessnig

>> Department of Pharmacy, Pharmacology and Toxicology Section

The major research areas of our groups within the CMBI focus on signaling events altered in common disorders (in particular anxiety and stress/trauma-related) as well as rare congenital disorders (neurodevelopmental syndromes including autism and epilepsy). Recently, this work is and was embedded in the FWF-funded Forschungsgruppe "Neurobiology of anxiety in autism spectrum disorders" (2022-2026), the Spezialforschungsbereich SFB F44 "Cell signaling in chronic CNS disorders" (2011-2019), the FWF-funded doctoral programs Signal Processing in Neurons (SPIN, 2007-2021) and CavX (doc.funds: Calcium Channels in Excitable Cells) as well as the EU-co-funded interdisciplinary PhD training programme ARDRE.

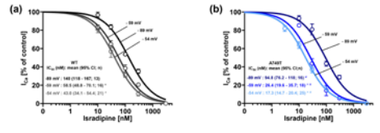
Neuropharmacology group (N. Singewald)

>> Goal: The group has focused on elucidating the neurobiological mechanisms underlying stress, anxiety and cognitive processes, aiming to identify novel therapeutic targets for neuropsychiatric disorders such as anxiety disorders, post-traumatic stress disorder (PTSD) and more recently also comorbid anxiety in individuals with autism spectrum disorder (ASD).

>> Background: We study such potential mechanisms in clinically relevant mouse models of pathological anxiety and genetic mouse models of ASD by using a range of behavioral, neurochemical, immunological and neurobiological methods. Translation of findings to humans is a particular important recent aim, which we pursue in collaborative efforts, for example with the Psychiatry Departments of the Medical University Innsbruck.

>> Research highlights and outlook: We could show that both dopamine and L-DOPA in the ventromedial prefrontal cortex rescues fear extinction deficits, while interventions like ghrelin receptor agonists or fasting failed to improve extinction in extinction-impaired mice. This highlights the specificity of neurotransmitter pathways in fear and memory modulation. Expanding on neuromodulation, we discovered that PACAP signaling via CRF neurons in the hypothalamic paraventricular nucleus is crucial for stress responses, and characterized the role of brain-derived neurotrophic factor (BDNF) in serotonergic neurons in fostering stress resilience and enhancing adult hippocampal neurogenesis. In the domain of psychopharmacology, we contributed to the development of novel chiral monoamine reuptake inhibitors, demonstrating how stereochemistry fine-tunes selectivity, and

helped to advance cognitive enhancer research by characterizing a novel modafinil analogue (CE-158) that improves social memory via enhancing dopamine in the nucleus accumbens. A major goal of the group has been to dissect the influence of neuroimmune interactions on anxiety. We revealed that innate high-anxiety behavior is associated with microglial activity in a sex-dependent manner, with minocycline modulating this effect, suggesting microglia as potential sex-dependent targets for anxiety treatment. Complementing this, we demonstrated that an enriched environment normalizes high anxiety-like behavior by attenuating aberrant neuroinflammatory responses, underscoring the importance of environmental modulation in mental health. Finally using a deep-learning-based automated cell identification method to enable brain-wide mapping of activation patterns we revealed differences in brain signal processing of anxiety in normotypic vs ASD individuals which could guide the development of more personalized treatment development highly demanded in this field.



Isradipine inhibition of Cav1.3 WT and A749T channels at different holding potentials. α1-subunits were co-expressed together with β2a and α2δ1-subunits in tsA-201 cells. 'Run-down'-corrected concentration-inhibition curves measured at the indicated HP are shown for wildtype (WT, a) and mutation A749T (b). Data points are presented as means ± SEM from at least 3 individual recordings for each isradipine concentration. Isradipine has higher apparent sensitivity for A749T channels, which can be explained by their higher sensitivity to voltage-dependent inactivation. This favours interaction of isradipine with inactivated, high affinity channel states (Török et al. Br J Pharmacol 182, 181-197, 2025, Epub 2024 Oct 7).

Molecular Pharmacology and Neurophysiology group (J. Striessnig, N. Ortner)

>> Goal: Understand the function, regulation and disease potential of voltage gated Ca^{2+} channels (Cavs) in human disease.

>> Background: Cavs mediate the activity-dependent Ca^{2+} influx into all electrically excitable cells. The fine-tuning of these signals is essential for many physiological functions. A major focus of our work is on channelopathies of the Cav1.3-subtype (*CACNA1D* gene). Rare de novo missense mutations in humans provide exciting new insight into their function and pathophysiology.

>> Research highlights and outlook: In the last years we continued our successful characterization of disease-causing mutations and confirmed the pathogenicity of mutations that enable enhanced Ca^{2+} channel activity (gain-of-function). This causes a neurodevelopmental disorder often together with neurological and endocrine dysfunctions (seizures, hypoglycemia, hyperaldosteronism). We established our lab as a world-wide competence center allowing us to collect genetic and clinical information to decipher the natural disease history and improve genetic diagnostics. The latter also includes improved in silico predictions of the pathogenicity of newly identified variants in patients using algorithms developed in collaboration with the Liedl-group in the CMBI. Moreover, we have successfully generated the first animal model for this disease which allows to identify altered signalling pathways underlying the pathogenic phenotype but to also investigate potential pharmacological therapies for mitigation of burdensome symptoms of affected individuals (like autoagressive behaviors, hyperactivity). We also found that currently available Ca^{2+} channel blockers are potent inhibitors also of mutated Cav1.3 channels but that inhibition of hyperactive channels would be limited to cells operating from more depolarized membrane potentials (Figure).

>> Research Grants

FWF DOC30 doc.fund, P35722, FWF P35087, FG 18-B, FG 3500, FWF P27809, Tiroler Wissenschaftsförderung (TWF, UNI-0404/2345), Erika-Cremer habilitation fellowship by the University of Innsbruck (N. Ortner)

>> Coworkers

Nadja Hofer (Ph.D. student), Karl Ebner (postdoc), Maria Kharitonova (postdoc), Simone B. Sartori (university assistant), Anupam Sah (postdoc), Conor Murphy (Ph.D. student), Thomas Keil (Ph.D. student), Veronica Fontebasso (Ph.D. student), Sinead Rooney (Ph.D. student), Anita Siller (Ph.D. student), Eva Maria Fritz (Ph.D. student), Yuliia Nikonishyna (Ph.D. student), Ferenc Török (Ph.D. student), Ludovica Filippini (Ph.D. student), Nino Kobakhidze (Ph.D. student), Horia Hermenean (Ph.D. student)

Structural biology, biophysical chemistry, NMR spectroscopy

Martin Tollinger

>> Department of Organic Chemistry

>> Goal: We investigate the structures and the folding behavior of RNA-binding proteins to understand their biological activity, employing integrated structural biology approaches.

>> Background: The three-dimensional structures of proteins determine how they interact with their biological targets (e. g., RNA). In addition, protein structural flexibility plays a key role in the binding process by enabling efficient recognition. Intrinsically disordered regions (IDRs) of proteins are of particular interest, as they can fold into secondary structures upon RNA binding, thereby providing the required intermolecular interactions. We use a range of complementary approaches to study the structures and structural flexibility of proteins and their interactions with RNA, with an experimental focus on NMR spectroscopy. NMR-based techniques provide high-resolution information on even low-populated structural features of proteins (and RNA) that are critical for binding and function. By integrating NMR data with X-ray crystallography and computational methods, we gain insights into how protein folding, RNA binding, and biological activity are interconnected.

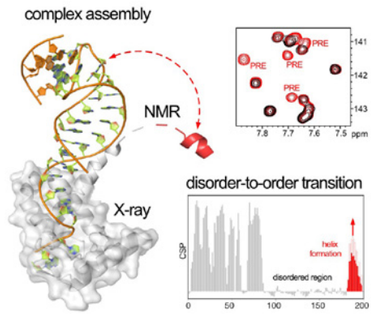
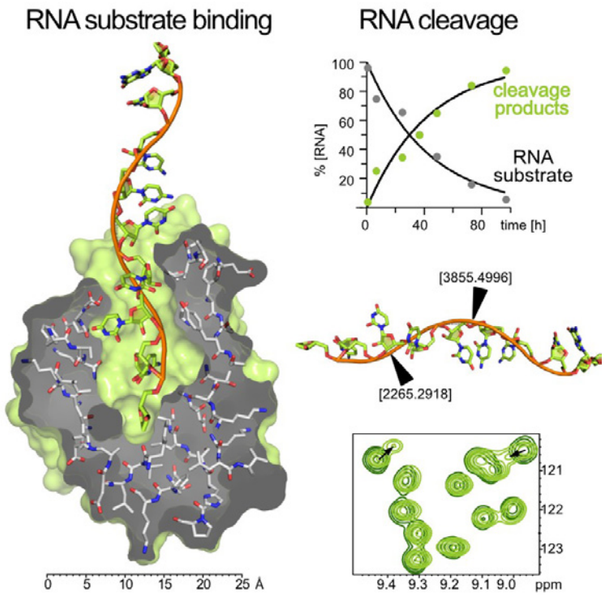


Figure 1. Combined X-ray and NMR structure of an RNA chaperone involved in bacterial horizontal gene transfer. X-ray crystallography reveals the chaperone's folded "binding platform" for RNA, while NMR spectroscopy provides site-resolved insights into intrinsically disordered regions and structural changes, such as helix formation upon RNA binding.

>> Research highlights and outlook: One focus of our laboratory is RNA chaperones that act as molecular switches in bacterial horizontal gene transfer. We experimentally characterize the structures and flexibility of different complex structures that are involved in the chaperoning process. Using NMR spectroscopy, we examine specific aspects of these systems and complement this information with other techniques. For example, paramagnetic relaxation enhancement (PRE) NMR is used to probe the IDRs of the chaperone, while chemical shift perturbation (CSP) mapping monitors helix formation during RNA binding and X-ray crystallography contributes the structure of the static RNA binding platform (Figure 1). Together, these data shed light on which structural elements (transiently) interact during complex formation. Future studies will focus on understanding the RNA chaperoning mechanism in detail.

Figure 2. Left: NMR structure of a PR-10 protein, which acts by degrading invading viral RNA in plants. This ribonuclease binds single-stranded substrate RNA into a binding pocket, priming it for enzymatic cleavage. Right: Details of the ribonuclease activity studied by mass spectrometry and NMR spectroscopy.



Another focus of our group is PR-10 proteins - ribonucleases that are upregulated in plants upon viral infection. NMR spectroscopy is used to determine the three-dimensional structures of these proteins in solution and to map the binding site of the RNA substrate. Results show that PR-10 proteins bind single-stranded RNA in a conserved binding pocket, priming it for enzymatic cleavage (Figure 2). The cleaved oligonucleotide is then bound again and further processed. The details of PR-10 ribonuclease activity are being investigated using mass spectrometry, revealing that these enzymes function as endonucleases that cleave single-stranded RNA into oligonucleotides. We are currently examining the RNA sequence specificity of these proteins.

>> Research Grants

FWF-P30963, FWF-P31054, FWF-33953

>> Coworkers

Matthias Huber, Manuel Röck, Jana Unterhauser, Ricarda Zeindl (PhD students); Alessia Karasani, Carolyn Lucy (Master students)

Role of voltage gated calcium channels in endocrine cells

Petronel Tuluc

>> Department of Pharmacy, Pharmacology and Toxicology Section

>> Goal: The Tuluc lab has two major research directions. 1) To characterize the pharmacological and pathophysiological roles of voltage-gated calcium channels (Ca_V) in various endocrine cells function and hormone secretion (pancreatic β-cells insulin release, adrenal chromaffin cells adrenalin secretion, adrenal zona glomerulosa (ZG) cells aldosterone synthesis and release). 2) To investigate how the biophysical properties of Ca_V channels are shaped by specific intramolecular interactions and disease-causing mutations.

>> Background: Calcium influx through Ca_V channels is critical for numerous cellular functions, including excitability, synaptic neurotransmitter release, muscle contraction, and hormone synthesis and secretion. Additionally, calcium influx plays a key role in regulating gene transcription, cell differentiation, and survival. Consequently, even minor alterations in Ca_V channel function or expression can result in significant physiological dysregulation and disease. Owing to their central role in cellular excitability and function, Ca_V channels are also important drug targets for both existing and emerging therapies.

>> Research highlights and outlook: In the last years we could demonstrate that:

The $\alpha_2\delta$-1 subunit on Ca_V channel is an important regulator of chromaffin cell excitability. $\alpha_2\delta$-1 deletion reduced MCC calcium influx but caused a paradoxical increase in cellular electrical activity as well as a higher frequency of induced adrenaline/noradrenalin vesicle release.

In pancreatic β-cells we could show that the female β-cells have a higher glucose-induced electrical activity and insulin release compared to males. The different β-cell membrane potential caused increased insulin release but reduced Ca_V channel availability and calcium influx conferring resistance to the development of T2DM for females.

In collaboration with the laboratory of M. Campiglio and B.E. Flucher (Dep. Of Physiology, Medical University of Innsbruck) we identified and characterized a new class of Ca_V channel interaction partners, the Stac proteins.

Using a global Stac2$^{-/-}$ mouse model we are currently investigating how Stac2 genetic ablation alters the electrical activity and adrenaline/noradrenaline secretion of chromaffin cell (Stefanie Geisler), pancreatic β-cell excitability and insulin release (Laura Häfele and Dorina Tota), as well as mouse behaviour and primary hippocampal neurons (Stefanie Geisler).

Besides being a critical modulator of Ca_Vchannel membrane incorporation and biophysical properties, the $\alpha_2\delta$-1 subunit is also the drug target for the antiepileptic and analgesics gabapentinoid compounds. Ryoichi Taguchi and Michaela Lettenbichler can demonstrate that gabapentin has a dual role on β-cell function increasing excitability but reducing insulin release.

In collaboration with Nadine J. Ortner we can show that mice carrying a patient-identified Ca_V1.3 gain-of-function mutation show significantly lower fasting plasma glucose levels and enhanced glucose tolerance in a sex-dependent manner. Current experiments are on the way to identify the molecular mechanism leading to this effect (Laura Häfele and Ryoichi Taguchi).

Continuing this line of research, we have established an FWF-funded CMBI research group (Forschungsgruppe F3500) between the institutes of Pharmacy and Molecular Biology. This interdisciplinary effort investigates the effect of Ca_V1.3 patient-derived mutations on neuronal iPSCs development (F. Edenhofer, C. Esk) and function (S. Geisler), mouse brain slices (N.J. Ortner - coordinator), and aldosterone secreting ZG cells (P. Tuluc).

>> Research Grants

FWF P36053, DOC178, FG3500 to PT; TWF F.18863 and F.49714/7-2023, NFB LSC19-017, FG3500 to SMG

>> Coworkers

Stefanie M. Geisler (postdoc), Laura Häfele, Ryoichi Taguchi (Ph.D. students), Michaela Lettenbichler, Dorina Tota, Caroline Margarethe Ploner (Master students)

Cell metabolism and differentiation research

Werner Zwerschke

>> Research Department for Biomedical Aging Research

>> Goal: The Zwerschke lab works on the biology of the adipose organ with main emphasis on molecular mechanisms regulating the fate of adipose stem/progenitor cells (ASCs). The group studies also the role of ASCs and adipocytes in aging and obesity working on weight-loss target genes and development of CR mimetics.

>> Background: Age-related changes in the adipose organ play a major role in aging and are detrimental for health. Major changes beginning already in midlifers are a decrease of the subcutaneous adipose tissue (sWAT) and rearrangements to more visceral and ectopic fat depots. This leads to reduced triglyceride storage capacity of the adipose organ, impaired metabolic performance and a low chronic inflammatory state. Similarly, obese people frequently show a phenotype of premature aging. In both scenarios, aging and obesity, a functional decline in ASCs and adipocytes plays an important part. The group studies genes in ASCs and adipocytes that are involved in cell fate control, aging, obesity and weight-loss. Moreover, the group fosters the development of CR mimetics. To address our research goals, we work with primary human cells in cell culture, adipose organoid models and genetic animal models. Moreover, we use genomics, transcriptomics and proteomics technologies, modern techniques of molecular and cell biology including lentivirus-based systems for infection of primary cells, RNA interference, CRISPR-mediated genome editing, flow cytometry and imaging technologies.

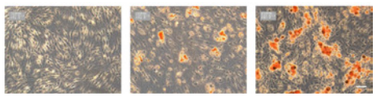


Figure 1: Adipogenesis in human ASCs: Staining of triglycerides by Oil Red O is shown at days d0, d9 and d14 of adipogenic differentiation. Scale bar 100 µm.

>> Research highlights and outlook: A major aim of our group is to better understand the impact of weight-loss interventions on ASCs. We made substantial progress in this research area by the identification of novel weight-loss target genes in human ASC. One of these genes is Sprouty1, a negative regulator of Ras-MAPK signalling. We demonstrate that Sprouty1 prevents cellular senescence maintaining proliferation and differentiation capacity of the ASCs and contributing to the maintenance of stemness in ASCs. Another weight-loss target gene identified in the period is the circadian transcription factor Aryl hydrocarbon receptor nuclear translocator-like 2 (ARNTL2). As major finding we show that ARNTL2 acts as inhibitor of adipogenesis in ASC. The heterogeneous ASC populations in sWAT is not yet precisely characterized. We demonstrate in a recent research project that cell surface expression of dipeptidyl peptidase-4 (DPP4) contributes to a better typification of human ASC in sWATs. We show that $DPP4^+$ ASCs possess higher self-renewal and proliferation capacity and lesser adipocyte differentiation potential than $DDP4^-$ ASCs underscoring the importance of DPP4 as functional marker for an abundant ASC population in human sWAT. In another research project, we established an adipose organoid model system for human ASCs. This model can now be used for functional studies in ASC differentiation. Finally, we studied the physiological role of alkylglycerol monooxygenase (AGMO) in lipid metabolism during adipogenesis in 3T3-L1 preadipocytes. The results suggest that alkylglycerol catabolism has an influence on ether-linked species and the degree of unsaturation in the amounts of triacylglycerols formed during adipocyte differentiation. In the future, the group will continue the work on weight-loss genes in human ASC and adipocytes and on the development of CR mimetics.

>> Research Grants

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>> Coworkers

Markus Mandl (postdoc); Florian Hatzmann (Ph.D. student), Camille Brucker (Ph.D. student), Sonja Großmann (Ph.D. student), Victoria Strobl (Ph.D.); Sonja Wagner, Valerie Schiller, Jochen Springer, Matthias Ensle-Weiß (Master students), Rebecca Baumgartner, Juliane Gasser (bachelor students); Hans-Peter Viertler, Petra Waldegger (Technicians)

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J. Striessnig, N. Singewald

Dannenberg F, Von Moers A, Bittigau P, Lange J, Wiegand S, Török F, Stölting G, Striessnig J, Motazacker MM, Broekema MF, Schuelke M, Kaindl AM, Scholl UI, Ortner NJ. A Novel De Novo Gain-of-Function CACNA1D Variant in Neurodevelopmental Disease With Congenital Tremor, Seizures, and Hypotonia. *Neurol. Genet.* **10**, e200186 (2024).

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P. Tuluc

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CMBI - Awards & Honors for CMBI Scientists

awards

Anna Ploner, Department of Organic Chemistry: Poster award, 9th Annual CMBI Meeting, Igls, Austria, 2024 (Abb.1)

Sarah Heel, Department of Organic Chemistry: Poster award, 8th Annual CMBI Meeting, Igls, Austria, 2022

Michael Palasser, Department of Organic Chemistry: Poster award, 12th conference on Isolated Biomolecules and Biomolecular Interactions (IBBI), Obergurgl, Austria, 2022

Matthias Achrainer, Department of Zoology: Best Poster Award at the meeting "Evolution of Resilience, Regeneration, and Animal Complexity – Insights from Basal Metazoans", September 18-21, 2023, Tutzing, Germany

Isabel Dittmann, Department of Zoology: Award of Excellence 2024 - Staatspreis für Dissertationen des Bundesministeriums für Bildung, Wissenschaft und Forschung (Abb.2, Quelle BfÖ, Uni Innsbruck)

Michele Petit/Alexander Weiss, Research Institute for Biomedical Aging Research: Tiroler Wissenschaftsfonds, Project "FAHD1 as a new therapeutic target in prostate cancer"

Maria Cavinato, Research Institute for Biomedical Aging Research: Tiroler Wissenschaftsfonds, Project "Molecular mechanisms of mitochondrial quality control in the process of photoaging of reconstructed human skin"

Sophia Wedel, Research Institute for Biomedical Aging Research: Swarovski grant "2D goes 3D: tBHP-induced senescence in fibroblasts potentially drives structural rearrangement of Skin and extrinsic Skin aging"

Maria Cavinato, Research Institute for Biomedical Aging Research: Award of best scientific presentation at the First World Congress on Targeting EVs (Malta – October 2024)

Minh Bui Hoang, Michael Popp Department: Poster Award, International Congress on Natural Products Research (ICNPR), Krakow, Polen, 2024 (Abb.3, Quelle Pharmakognosie)

Finja Witt, Michael Popp Department, Poster Award: 7th International Symposium on Phospholipids in Pharmaceutical Research, Heidelberg, Germany, 2022 (Abb.4, Quelle Phospholipid Research Center)

Solveigh Koeberle, Michael Popp Department: Travel Award, International Conference of Trace Elements and Minerals (ICTEM), Aachen, Germany, 2022

Thomas Magauer, Department of Organic Chemistry: Research Award by the Südtiroler Sparkasse (2023)

Jan Paciorek, Department of Organic Chemistry: TWF Projekt (2024)

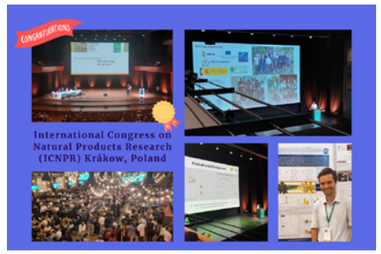
Immanuel Plangger, Department of Organic Chemistry: TWF Projekt (2023); CMBI Speaker Award (2024) (Abb.1, Quelle CMBI)

Nicolas Müller, Department of Organic Chemistry: TWF Projekt (2022)

Liesa Röder, Department of Organic Chemistry: TWF Projekt (2022)

Anna Ploner, Immanuel Plangger (Abb.1)

Isabel Dittmann (Abb.2)



Minh Bui Hoang (Abb.3)

Finja Witt (Abb.4)

Dr. Lukas Wein (Abb.5)

Dr. Lukas Wein (Abb.6)

Fabian Jürgen Hammerle (Abb.7)

Lukas Wein, Department of Organic Chemistry: Erwin Schrödinger Fellowship (2022); Hypo Tirol Bank Dissertationspreis (2023) (Abb.5, Quelle BfÖ, Uni Innsbruck)
Sosnovsky Award (2023) (Abb.6, Quelle BfÖ, Uni Innsbruck)

Tobias Pinkert, Department of Organic Chemistry: ESPRIT Program (2020)

Ondrej Kovac, Department of Organic Chemistry: Experientia Postdoctoral Fellowship (2020)

Julia Thaler, Department of Organic Chemistry: Travel Award, 8th Cambridge Symposium on Nucleic Acids Chemistry and Biology, 17-20 September 2024, Cambridge, United Kingdom, 2024

Sarah Moreno, Department of Organic Chemistry: Monatshefte für Chemie / Chemical Monthly – Young Scientists Best Paper Award 2023

Laurin Flemmich, Department of Organic Chemistry: IRT Travel Award 2022 – International Round Table on Nucleosides, Nucleotides and Nucleic Acids, IRT3NA – August 28-31, 2022, Stockholm, Sweden

Michaela Egger, Department of Organic Chemistry: IRT Poster Prize – International Round Table on Nucleosides, Nucleotides and Nucleic Acids, IRT3NA – August 28-31, 2022, Stockholm, Sweden

Mark J Horgan, Pharmacognosy Section: Kelvin Chan Prize for Best Presentation: "Anthelmintic activity of alpine cultivated *Cicerbita alpina*", Third Annual Conference on Natural Products (2022)

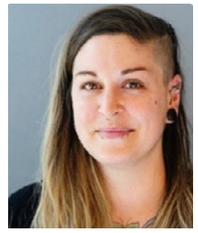
Mostafa Alilou, Pharmacognosy Section: Pharmacologically active plant constituents used in traditional medicine - Isolation and structure elucidation with special focus on chiroptical methods and NMR chemical shift calculation. 8 / 13. Leopold-Franzens-Universität Innsbruck - Vizerektorat für Forschung, Hypo Tirol Bank Dissertationspreis (2022)

Fabian Jürgen Hammerle, Pharmacognosy Section: Studies on the phenomenon of photoactivity in the genus Cortinarius and other basidiomycetes. Studien über das Phänomen der Photoaktivität in der Gattung Cortinarius und anderen Basidiomyceten. Leopold-Franzens-Universität Innsbruck - Vizerektorat für Forschung, Award of Excellence (2023)

Fabian Jürgen Hammerle, Pharmacognosy Section: MDPI Separations Young Scientist Session Award (best oral presentation) at the 33rd International Symposium on Pharmaceutical and Biomedical Analysis, 2-6 July 2023, Ankara, Türkiye (2023)

Fabian Jürgen Hammerle, Pharmacognosy Section: Studies on the phenomenon of photoactivity in the genus Cortinarius and other basidiomycetes. Leopold-Franzens-Universität Innsbruck - Vizerektorat für Forschung, Hypo Tirol Bank Dissertationspreis (2023) (Abb.7, Quelle BfÖ, Uni. Innsbruck)

Bianka Siewert, Pharmacognosy Section and Department of Microbiology: Egon-Stahl-Award in Silver: Distribution and pharmaceutical potential of polyketide photoantimicrobials from Cortinariaceae (2023)



Nadine Ortner

Marcel Tisch

Angeliki Spathopoulou

Nadine Ortner

Bianka Siewert, Pharmacognosy Section and Department of Microbiology: Habilitation. Distribution, ecological function, and pharmaceutical use of fungal photosensitizers. Leopold-Franzens-Universität Innsbruck - Vizerektorat für Forschung, Preis der Landeshauptstadt Innsbruck für die wissenschaftliche Forschung an der Universität Innsbruck (2023)

Minh Bui Hoang, Pharmacognosy Section: Poster Award - International Congress on Natural Products Research (2024)

Nadine Ortner, Department of Pharmacy, Section of Pharmacology and Toxicology, is recipient of the 2023 Heribert Konzett Award. The Heribert Konzett Award is awarded annually by the Austrian Pharmacological Society (APHAR) in order to honour outstanding achievements of young scientists who are already conducting independent research in the field of experimental and clinical pharmacology as well as clinical pharmacology and to support their further career.

Marcel Tisch, Institute of Molecular Biology: Best poster award, 8th CMBI Meeting, University of Innsbruck (2022)

Marcel Tisch, Institute of Molecular Biology: Best poster award, PhD Life Science Meeting, University of Innsbruck (2023)

Marcel Tisch, Institute of Molecular Biology: GSCN travel award, University of Innsbruck (2023)

Angeliki Spathopoulou, Institute of Molecular Biology: Understanding cellular rejuvenation by single cell multi-omics profiling, University of Innsbruck (2024)

Angeliki Spathopoulou, Institute of Molecular Biology: ARDRE Winter School Best Talk Award, University of Innsbruck (2024)

Angeliki Spathopoulou, Institute of Molecular Biology: CMBI Best Talk Award, University of Innsbruck (2024)

Gabassi Elisa, Institute of Molecular Biology: AGE_REG Summer School 2024: runner-up best presentation award, University of Innsbruck (2024)

Gabassi Elisa, Institute of Molecular Biology: ISSCR Merit Award, University of Innsbruck (2024)

TWF projects were awarded to the following researchers:

2021

Prem Eva Maria, Department of Microbiology: The effects of phenyl acids on the anaerobic microbial community at different pH regimes

Geisler Stefanie, Pharmacology and Toxicology Section, Department of Pharmacy: Role of the calcium channel subunit alpha(2)delta-1 in chromaffin cell catecholamine secretion and blood pressure regulation

Kaserer Teresa, Pharmaceutical Chemistry Section, Department of Pharmacy: Identifying and overcoming next generation c-Kit inhibitor resistance mutations in cancer therapy

Kwiatkowski Marcel Dominik, Department of Biochemistry: Yin Yang - the AKT-TSC-mTORC1 axis: The coupling of energy metabolism and the protein acylome in tuberous sclerosis complex disease

Ramos Pittol Jose Miguel, Department of Biochemistry: Effects of chronic mTORC1 activation in hepatic FXR signalling

Wein Lukas Anton, Department of Organic Chemistry: Totalsynthese der Diterpenoide Mitrephorone A-C

Jäger Stefanie, Department of Zoology: Physiologisches Wettrüsten von Stechmücken als potentielle Gefahr für den Menschen

2022

Zeng Fan, Department of Zoology: Chasing the Ciona intestinalis larval glue

Bertemes Philip, Department of Zoology: Genome sequencing using ultra-long reads for the discovery of novel bioadhesive proteins

Martic Ines, Research Department for Biomedical Aging Research: tBHP vs. UVB: how different environmental stressors affect melanocytes

Zeindl Ricarda, Department of Organic Chemistry: Functional structural flexibility of camelid nanobodies studied by NMR spectroscopy

Filippini Ludovica, Department of Pharmacy, Dep. of Pharmacology and Toxicology: Towards a Cav1.3 - selective antagonist

Röder Liesa, Department of Organic Chemistry: A Nazarov-Type Polyene Cyclization Strategy for the Total Synthesis of Tetracyclic Triterpenoids

Hammerle Fabian Jürgen, Department of Pharmacy: AMPlify - Natural Products for Anti-Malaria Photodynamic Therapy

Rao Zhigang, Michael-Popp-Research Department: Communication between the immune microenvironment and ferroptotic cancer cells

Bartosik Karolina, Department of Organic Chemistry: Development of New Methods for the Synthesis of Cyclic Oligoribonucleotides

Zanetti Lucia, Department of Pharmacy, Dep. of Pharmacology and Toxicology: Validation of viral vectors for gene supplementation of Cav1.4 L-type calcium channels in retinal disease

Müller Nicolas, Department of Organic Chemistry: Enantioselective Synthesis of Ganoderma Meroterpenoids: Total Synthesis of Ganoapplanin

Heberle Alexander Martin, Department of Biochemistry: Novel mTOR complexes integrate RNA metabolism

2023

Gregor Andreas Pichler, Department of Botany: Der isolierte Mykobiont der Flechte Cetraria islandica: Isolierungstechniken, Kultivierung und Sekundärmetaboliten

Nicole Schmitner, Department of Molecular Biology: Regulierung und Modulation der Glucokinase zur Behandlung von Diabetes

Bernhard Manuel Kriesche, Department of General, Inorganic and Theoret. Chemistry, Department of Theoretical Chemistry: Entwicklung, Implementierung und Anwendung neuartiger Ansätze des maschinellen Lernens für supramolekulare Verbindungen

Immanuel Plangger, Department of Organic Chemistry: Totalsynthese von ent-Pimaranen als Screening-Plattform für neue entzündungshemmende und krebsbekämpfende Arzneimittel

Ulrike Rehbein, Department of Biochemistry: Kontrolle des auditorischen Hirnstamms und der Verhaltensmerkmale durch den metabolischen Hauptregulator mTORC1

2024

Florian Hatzmann, Department of Biochemistry: Lipolysis versus Lipogenesis - Elucidating Alterations in Lipid Metabolism in Tuberous Sclerosis Complex

Yang Zhang, Department of Biochemistry: A novel Multi-Omics mTOR Signature

Tobias Kipura, Department of Biochemistry: CrossAct - Deciphering PTM crosstalk and Histone Acetylation Dynamics

CMBI - Careers

Faculty appointment

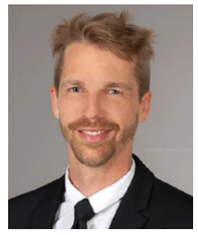
Francesca Finotello earned her PhD in Bioengineering in 2014 at the University of Padova, Italy. She is an Assistant Professor at the Institute of Molecular Biology and Digital Science Center (DiSC) of the University of Innsbruck, Austria, where she leads the Computational Biomedicine group. She has longstanding expertise in the bioinformatic analysis of bulk and single-cell multiomics data and in the development of computational methods to inform precision and personalized medicine. Her group has a particular focus on cancer immunology and integrates bioinformatics, systems biology, and machine learning techniques to elucidate the rules governing tumor-immune cell interaction. By characterizing the landscape of cancer neoantigens, the composition of the tumor immune contexture, and the intricate crosstalk governing cell-cell interactions in the tumor microenvironment, she aims at extracting mechanistic rationale to improve cancer immunotherapy.

Christopher Esk is an assistant professor in the Institute of Molecular Biology at the University of Innsbruck, Austria. Christopher studied Biochemistry in Hannover, Germany and performed his graduate studies at the University of California, San Francisco, USA. He moved to a postdoctoral position at the Institute of Molecular Biology in Vienna, Austria before joining the University of Innsbruck in 2021. He uses 3D cell culture models combined with genetic tools to understand aspects of human brain development.

Faculty appointment

Solveigh Koeberle has been setting up her own research group at the Michael Popp Institute for Plant-Based Drug Research at the University of Innsbruck. From 2022 - 2024, she has also been appointed as interim professor for the Chair of Medicinal Chemistry at the University of Regensburg.

Her research, which is meanwhile funded by the renowned Elise Richter Program of the Austrian Science Fund (FWF), focuses on the development of innovative drug candidates, the elucidation of molecular targets and disease mechanisms, and the exploration of novel therapeutic approaches for degenerative diseases such as metabolic-associated fatty liver disease (MAFLD), Alzheimer's and Parkinson's, with a particular focus on ferroptosis-inhibiting natural products.



Faculty appointment

Gregor Pichler moved from the Department of Botany to the HBLFA Schönbrunn, Department of Agriculture, Forestry, Regions and Water Management, Federal Ministry Republic of Austria, where he heads a research group for plant protection.

Faculty appointment

Simone Moser is Professor of Pharmacognosy at the University of Innsbruck since September 2023, and joined the CMBI in 2024. She is investigating the new natural substance class of phyllobilins, which are produced during the ageing process of plants.

Simone Moser specializes in a new class of active ingredients that are produced during the ageing process of plants: phyllobilins. "Phyllobilins are tetrapyrroles that are produced in plants when the green pigment chlorophyll is broken down," she explains. These degradation products were long regarded as pure waste products. "However, phyllobilins actually have an important function. Some of these molecules have antioxidant properties that can help protect plant cells from damage caused by free radicals."

During her time as a research group leader at LMU Munich, Simone Moser has already carried out several structural elucidations of phyllobilins and was able to prove, for example, that antioxidant and anti-inflammatory active ingredients can be found in stinging nettle tea. "We have also found phyllobilins that have shown an effect on cancer cells," explains Moser. She wants to investigate this effect in greater depth using a test method that the scientist has further developed for this new class of natural substances. The Yeast Three-Hybrid System can be used to investigate the interactions of molecules in yeast cells. "In the search for active substances, the question is whether a potential active substance interacts with a so-called target - a target protein in the body that is associated with the disease," explains Simone Moser. "The special thing about the Yeast Three-Hybrid System is that we can not only investigate the interaction between a natural substance and a target protein, but also test many different target proteins at the same time," says the scientist. "This means that we can test thousands of potential interactions in one experiment." Simone Moser would like to continue using this method to explore the potential of ageing products from plants as lead structures for interesting therapeutic applications.

Simone Moser studied chemistry at the University of Innsbruck and, after completing her doctorate, spent several years researching at the EPFL in Lausanne and MIT in Cambridge, Massachusetts. After a period in Analytical Development at Sandoz in Langkampfen, she finally set up her own research group at the Chair of Pharmaceutical Biology at the LMU Munich, where she habilitated in 2022. Simone Moser has received several awards for her work on the pharmaceutical effects of newly discovered natural products, including the Blair-Curtius-Pfleiderer-Wachter Prize for Pteridinology in 2020 and the Dr. Willmar-Schwabe Prize of the Society for Medicinal Plant and Natural Product Research in 2022.

https://www.uibk.ac.at/de/newsroom/2023/vorgestellt-pflanzliche-abbauprodukte-als-chance/

CMBI - meetings

meetings

External speakers at previous CMBI meetings

In addition to the many exciting short talks and poster presentations from members of the CMBI and the Biocenter, guest lectures from invited top scientists contributed to the lively discussions. Like in previous meetings, the speakers also served as advisory experts for our research activities and as referees for the poster awards for young scientists.

8th CMBI Meeting Innsbruck, Igls, Tyrol, September 30th, 2022
>> Nuno Maulide
Department of Organic Chemistry, University of Vienna, Austria
>> Sabrina Büttner
Department of Molecular Biosciences, Stockholm University, Sweden
>> Anjali M. Rajadhyaksha
Molecular and Developmental, Neuroscience Laboratory, Pediatric Neurology, Pediatrics, Brain and Mind Research Institute, Weill Cornell Medicine, New York, USA

7th CMBI Meeting Innsbruck, Innsbruck, Tyrol, September 19th - 20th, 2018
>> Zlatko Trajanoski
Division of Bioinformatics, Medical University of Innsbruck
>> Martina Höckner, Department of Zoology, University of Innsbruck
>> Hashim M Al-Hashimi
Department of Biochemistry, Duke, University Medical Center, Durham North Carolina, US

6th CMBI Meeting Innsbruck, Innsbruck, Tyrol, March 3th - 4th, 2016
>> Christian Griesinger
Max Planck Institute for Biophysical Chemistry Göttingen, Germany
>> Frank Edenhofer, University of Innsbruck, Austria
>> Remco Sprangers, Max Planck Campus Tübingen, Germany
>> Almut Schulze, University of Wuerzburg, Germany

7th Life Science Meeting Innsbruck, Innsbruck, Tyrol, Feb. 27th, 2015
>> Peter Hinterdorfer, University of Linz, Austria
>> Eduard Stefan, University of Innsbruck, Austria
>> Peter Ladurner, University of Innsbruck, Austria
>> Gunter Meister, University of Regensburg, Germany
>> Gerald Obermair, Medical University of Innsbruck, Austria
>> Natascha Kleiter, Medical University of Innsbruck, Austria
>> Pascal Meier, ICR London, UK
>> Marlies Meisl, University of Chicago, USA
>> Martin Puhr, Medical University of Innsbruck, Austria
>> Bill Earnshaw, University of Edinburgh, UK

6th Life Science Meeting Innsbruck, Innsbruck, Tyrol, Sept. 24th - 25th, 2014
>> Robert T. Batey, University of Colorado Boulder, USA
>> Veronika Sexl, University of Veterinary Medicine, Vienna, Austria
>> Florian Kronenberg, Medical University of Innsbruck, Austria

5th Life Science Meeting Innsbruck, Innsbruck, Tyrol, Sept. 25th - 27th, 2013
>> Asifa Akhtar
Max Planck Institute of Immunobiology and Epigenetics, Germany
>> Michel Desjardins, Universite de Montreal, Canada
>> Carl-Philipp Heisenberg, IST Austria
>> Karolin Luger, Colorado State University, USA
>> Frauke Melchior, ZMBH Heidelberg University, Germany
>> Nikolaus Pfanner, University of Freiburg, Germany
>> Britta Qualmann, Friedrich-Schiller-University Jena, Germany
>> Elena Rugarli, University of Cologne, Germany
>> Susan S. Taylor, University of California San Diego, USA

4th Life Science Meeting Innsbruck, Igls, Tyrol, Sept. 27th - 28th, 2012
>> Christine Foyer
Centre for Plant Sciences, University of Leeds, United Kingdom
>> Ari Helenius, Institute of Biochemistry, ETH Zürich, Switzerland
>> Anne-Claude Gavin
Structural and Computational Biology, EMBL Heidelberg, Germany

3rd Life Science Meeting Innsbruck, Igls, Tyrol, Sept. 23th - 24th, 2011
>> Ilme Schlichting
Department of Biomolecular Mechanisms, Max Planck Institute for Medical Research, Heidelberg, Germany
>> Adrian R. Ferré-D'Amaré
Laboratory of RNA Biophysics and Cellular Physiology, Biochemistry and Biophysics Center, National Heart, Lung and Blood Institute, Bethesda, USA
>> Daniel Minor
Cardiovascular Research Institute, Departments of Biochemistry & Biophysics, and Cellular & Molecular Pharmacology California Institute for Quantitative Biomedical Research, University of California, San Francisco, USA

2nd Life Science Meeting Innsbruck, Igls, Tyrol, Sept. 24th - 25th, 2010
>> Maria Sibilia
Institute for Cancer Research, Medical University of Vienna, Austria
>> Adriano Aguzzi
Institute of Neuropathology, University Hospital of Zürich, Switzerland
>> Rik Korswagen
Hubrecht Institute, Utrecht, Netherlands

1st Life Science Meeting Innsbruck, Igls, Tyrol, Sept. 18th - 19th, 2009
>> Dirk Trauner
Department of Chemistry and Biochemistry, LMU Munich, Germany
>> Didier Stainier, University of California, San Francisco, USA
>> Wolfgang Baumeister
Max-Planck-Institute of Biochemistry, Martinsried, Germany

CMBI - meetings

meetings

5th Annual CMBI-Meeting Igls, Tyrol, Sept. 26th - 27th, 2008
>> Peter Hegemann
Institute for Biology, Experimental Biophysics, Humboldt University Berlin, Germany
>> Stefan Schulte-Merker
Hubrecht Laboratory, Netherlands Institute for Developmental Biology Utrecht, Netherlands

4th Annual CMBI-Meeting Igls, Tyrol, Sept. 28th - 29th, 2007
>> Ulf R. Rapp
Medical Radiation & Cell Research, Univ. of Würzburg, Germany
>> Gregory J. Kaczorowski
Merck Research Laboratories, Rahway, New Jersey, USA
>> Thomas W. Holstein
Institute of Zoology, University of Heidelberg, Germany

3rd Annual CMBI-Meeting Vill, Tyrol, Sept. 29th - 30th, 2006
>> Naweed I. Syed, Anatomy and Physiology, University of Calgary, Canada
>> Erwin F. Wagner
Research Institute of Molecular Pathology, Vienna, Austria
>> Walter Schaffner
Institute of Molecular Biology, University of Zurich, Switzerland

2nd Annual CMBI-Meeting Vill, Tyrol, Sept. 30th - Oct. 1st, 2005
>> Wolfram Saenger
Inst. of Chemistry & Crystallography, Free University Berlin, D
>> Peter Herrlich, Institute of Molecular Biotechnology, Jena, Germany
>> Elisabeth Knust, Institute of Genetics, University of Düsseldorf, Germany

1st Annual CMBI-Meeting Vill, Tyrol, Oct. 1st - 2nd, 2004
>> Robert Huber
Nobel Laureate in Chemistry, MPI of Biochemistry, Martinsried, D
>> Reinhard Fässler
Max-Planck-Institute of Biochemistry, Martinsried, Germany
>> Daniela Pietrobon
Dept. of Biomedical Sciences, University of Padova, Italy

CMBI - seminar series

seminars

The CMBI seminars are a very important integrative and multidisciplinary activity of the CMBI and are also part of the PhD programs established within the CMBI. So far, it hosted 142 lectures from renowned scientists from the US, Canada, Australia, Sweden, Denmark, Netherlands, Poland, France, Italy, UK, Germany, Belgium, Switzerland, Israel, Finland, Japan, Luxembourg, Spain, Hungary, and Austria. It also provides a forum for excellent scientists from the Innsbruck Universities. Seminar speakers of the last three years are listed here:

2024

Karl Gademann, PhD.
Department of Chemistry, University of Zurich, CH
Thomas Kietzmann, PhD.
Faculty of Biochemistry and Molecular Medicine, University of Oulu, Finland
Terrance Snutch, PhD.
Department of Psychiatry, The University of British Columbia, Vancouver, Canada
Marcel Kwiatkowski, PhD.
Department of Biochemistry, University of Innsbruck, A
Jens Wöhnert, PhD.
Goethe Universität Frankfurt am Main, D
Hiroshi Abe, PhD.
Department of Chemistry, Nagoya University, Japan
Werngard Czechtizky, PhD.
Head of Medicinal Chemistry, Respiratory & Immunology, AstraZeneca, Sweden
Simone Moser, PhD.
Department of Pharmacy, Pharmacognosy, University of Innsbruck, A
Ulrich Stelzl, PhD.
Institute of Pharmaceutical Sciences, Pharmaceutical Chemistry, University of Graz, A
Valery Krizhanovsky, PhD.
Department of Molecular Cell Biology, Weizmann Institute of Science, Israel

CMBI - seminar series

seminars

2023

Susan Taylor, PhD.
University of California, San Diego, United States
Teresa Kaserer, PhD.
Institute of Pharmacy, Pharmaceutical Chemistry, University of Innsbruck, A
Andreas Marx, PhD.
Department of Chemistry, University of Konstanz, Germany
Gisbert Schneider, PhD.
ETH Zurich, Department of Chemistry and Applied Biosciences, Zurich, Switzerland
Yury Polikanov, PhD.
Department of Biological Sciences, University of Illinois at Chicago, USA
Bianka Siewert, PhD.
Institute of Pharmacy, Pharmacognosy, University of Innsbruck, A
Tsuyoshi Momose, PhD.
Institut de la Mer de Villefranche, Villefranche-sur-Mer Cedex, France
Sabine Fuchs, PhD.
Associate Professor, Pediatrician for metabolic diseases, UMC-Utrecht, NL
Pascal Meier, PhD.
Head of Cell Death and Immunity Team, Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London, UK
Alpaslan Tasdogan, PhD.
Institute for Tumor Metabolism, Department of Dermatology, University Hospital Essen, D
Christian Gruber, PhD.
Center for Physiology and Pharmacology, Medical University of Vienna, A
Jacek Jemielity, PhD.
Centre of New Technologies, University of Warsaw, PL

2022

Natalia Ivleva, PhD.
Institute of Analytical Chemistry and Water Chemistry, Technical University of Munich, D
Daniel Abankwa, PhD.
Full professor in Cellular Tumour Biology, Université du Luxembourg, L
Joern Dengjel, PhD.
Department of Biology, Université de Fribourg, CH
Maria Mittelbrunn, PhD.
Head of Immunometabolism and Inflammation Lab, Miguel Servet Researcher, Instituto de Investigación Hospital 12 de Octubre; Associate Professor, Molecular Biology Department, Universidad Autónoma de Madrid; ERC Researcher, Centro de Biología Molecular Severo Ochoa, Spain
Attila Szücs, PhD.
Eötvös Loránd University, Department of Physiology and Neurobiology, Budapest, Hungary

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contact

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